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PHYSIOLOGICAL MECHANISM OF EXPECTORATION[1,2]

HARRY C. BALLON

In this presentation I shall endeavor to assemble parts which may be regarded as mutually adapted and fitted to work together. It is hoped the finished product will be a theoretically functioning mechanism. Expectoration has been defined as the ejection from the mouth of material brought into it from the air passages. Such a definition does not serve our purpose for we are concerned with how material is cast off or rejected by the lung and bronchial tree. How mucus and other secretion are discharged or thrown (expectorated) *ex pectore* out of the breast (chest), is the question which has been raised and to which I shall attempt a reply. It will be necessary to consider many factors in order to obtain an answer.

There exists some element of doubt as to just how so-called heart failure cells reach the sputum. Be this as it may, it cannot be denied however that iodized oil stained with sudan III is ejected from the lung proper, long after the previously outlined bronchial tree is free of the radiopaque oil which now can be recognized radiologically only in the pulmonary parenchyma and histologically is found to be situated in the alveoli. Thus we have a right to proceed to a consideration of how secretion or material injected into the lung are propelled into larger bronchi. Particular emphasis is laid upon the term larger bronchi for, although cough can and does play an important rôle in the mechanism of expectoration as far as the major portion of the tracheobronchial tree is concerned, one must look elsewhere for an explanation as to how secretion escapes out of the alveoli and finer bronchi. The truth for this statement lies in the fact that whereas direct stimulation of the trachea, carina or larger bronchi can initiate the cough reflex, direct stimulation of the lung proper or finer ramifications of the bronchial tree does not provoke a similar response. To verify this statement one has but to introduce a sound into an experimentally produced bronchial fistula

[1] From the Department of Surgery, Jewish General Hospital, Montreal, Quebec.

[2] Read as part of a Symposium on *Sputum* at the Tuberculosis Sanatorium Conference of Metropolitan New York, Cornell Medical School, New York City, October 3, 1938.

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which concerns one of the terminal bronchi. Cognizance has been taken of the fact that stimulation of the pleura under abnormal circumstances may set up the cough reflex.

Respiration in general, collateral respiration, posture, ciliary motion, and changes in the size and shape of the bronchi, among other changes, may be called upon to aid us in the establishment of some sort of link between the lung and finer bronchi, and that point in the pathway of expectoration where the cough reflex becomes active.

The size of this presentation being of necessity limited, I shall consider in particular only ciliary motion and the bronchomotor apparatus.

Ciliated cells which arise from the intermediate cells and which as a result of mucous degeneration are probably represented by goblet cells as well, exceed the basal and intermediate cells in number. At the place where the ducts coming from the mucous glands enter the bronchi, the ciliated cells line the trumpet-shaped opening and extend into the duct (William Snow Miller). Although a so-called neuromotor organ responsible for ciliary motion has been suggested, no direct innervation or influence by a reflex nervous mechanism has been established. Nerve stimulation merely increases the amount of mucus which is poured out. Mucus apparently forms a suitable medium for the vibrating cilia (Lucas and Douglas). Cilia are easily fatigued. Temperature changes, particularly cold, diminishes their activity. According to Gordonoff ciliary motion is most active at between 37° to 40°C. Ciliary activity varies with pressure changes of respired air (variations in intrapulmonic pressure). Carlson, Wilson, Graham and I found that oil placed upon the mucosa of the excised trachea of the dog may be transported at the rate of 1 cm. in eighty seconds when the trachea is in a horizontal position. According to Lucas and Douglas the normal rate of ciliary vibrations in the trachea of the turtle studied *in situ* at a temperature of about 30°C. was 2.2 to 5.5 times per second. This frequency cannot be appreciably affected by drugs. Ciliated cells are easily injured.

From what has been stated it might be erroneously concluded that the ciliated cells are unfit to carry on any important function. Such is not the case; their vibrations are in the right direction. Cilia are stimulated by secretion with which they come in contact and which in turn is driven through the bronchial passages by the aid of ciliary motion and available air, etc. The ciliated cells undoubtedly play a part in the mechanism of expectoration.

It should be noted that no attempt has been made here to estimate

quantitatively the amount of injected material which is expectorated. In the case of iodized oil it is not nearly as much as one might imagine. In addition to what is expectorated, loss of material occurs in other ways. Thus there is a rise in the blood iodine. Phagocytosis and lung ferments among others also play a part in the preparation. Guernon and I are at present working with a pig lung extract. We have thus far not been impressed by the degree of activity of fat splitting ferments present in the lung (lipolytic activity).

I do not wish to enter into any controversy about whether or not alveolar pores (openings by which an alveolus communicates with an adjoining alveolus) are to be regarded as normal structures. I would like to mention, however, that Kohn found in cases of pneumonia that fibrin threads could be traced through minute openings in the alveolar wall from an alveolus into the adjoining alveolus.

Expectoration under ordinary circumstances gets away to a slow start. The fact that expectoration is frequently most profuse in the morning is an interesting reflection upon this point. I should like to elaborate further upon the slowness of expectoration.

Some years ago Jacobaeus, Selander and Westermark investigated the emptying capacity of the bronchi and lungs following the injection of lipiodol stained with sudan III. These studies were carried out upon patients. Jacobaeus and his coworkers were of the opinion that they could distinguish two phases in the expectoration of the stained oil. The first phase was regarded as an expression of the emptying capacity of the bronchi; the second as corresponding with the emptying of the finest bronchioles and alveoli. The second phase was found to be slower than the first and incomplete. The primary phase under normal conditions lasts from four to eight hours. This primary phase is occasionally followed by a transitional period of from eight to twelve hours during which time globules of lipiodol are still expectorated and coughed up. The second stage characterized by the presence of spots or streaks of oil in the sputum can be observed over a period of several days and does not follow any regular or constant course.

When I repeated these experiments ten years ago I experimentally demonstrated that sudan III did not produce any ill effects. There was no evidence of proliferative reaction following its use. It was found, however, that expectoration of nonstained sputum free of oil occurred and continued during a period when the oil could be visualized clearly roentgenologically. This state of affairs was particularly striking in the

presence of dilated bronchi. To repeat, if one injects the lung with oil it is possible to observe bronchi still injected for a considerable period. There need not be any apparent loss of any stained lipiodol during a period when there is abundant nonstained expectoration presumably from the injected portion of the lung. It is possible but unlikely that the oil may merely coat the bronchus and that unstained expectoration may come through such a coated bronchus. I also found that so-called expectoration time could vary in the same individual. This variability is to some extent dependent upon the amount of oil injected and its viscosity. It is well to remember, too, that this variation may be more pronounced in the presence of disease, for lipiodol may only sink to the bottom of dilatations after several days.

Bullowa and Gottlieb, Reinberg, Lorey and Brauer and others have all described certain movements of the trachea and bronchi which they regard as evidences of bronchial peristalsis. To my mind, whether or not one accepts the existence of bronchial peristalsis or peristaltoid movements of the bronchi is unimportant in this discussion. Certain uncontroversial all important facts remain. These are that the bronchi undergo changes in size and shape with respiration. These changes can be brought about alternately by the stimulation of certain nerves. In this connection a not altogether unimportant fact to which I first made reference elsewhere in 1928 (Frankfurt. Ztschr. f. Path., *36*, 207) is that, if iodized oil is injected into the bronchial tree of a rabbit fluoroscopically controlled, one frequently observes that before the oil, which some may regard as a foreign body, enters into the alveoli some of it may be shot back into the trachea and thence into the stomach. Some may regard such a phenomenon as evidence of bronchial peristalsis. I prefer to regard it as an expression of activity on the part of the bronchomotor apparatus.

That bronchopulmonary smooth muscle starts in the larynx and ends in the lung proper (Baltisberger) cannot be denied. And let us not forget that Grancher found that in bronchi 10 mm. in diameter the smooth muscle was 0.2 mm. in thickness; in bronchioli 1 mm. in diameter, the muscle was 0.1 mm. in thickness, five times as strong. If we now consider the excellent work of Luisada, it will be found that he clearly demonstrated by electrobronchographic records that bronchopulmonary smooth muscle by its contraction during expiration actively assists in expelling air from the lung. He found further that the amplitude of the electrobronchogram varied directly with the amplitude of respiration but

indirectly with the rate of respiration. The amplitude of the electrobronchogram curve increased as a result of vagal stimulation and diminished as a result of vagal inhibition or sympathetic stimulation. Luisada also showed that in normal respiration there is a pulmonary systole which occurs during expiration and a pulmonary diastole which occurs during inspiration. The close reflex relationship between bronchopulmonary smooth muscle, nasal and pharyngeal mucosa was again confirmed.

The existence of a bronchomotor pulmonary apparatus admirably constructed and adequately suited to facilitate the expulsion of secretion from the tracheobronchial tree thus appears evident. The fact that so few foreign bodies which are aspirated into the bronchial tree are coughed up reflects perhaps upon the efficiency of the cough mechanism, but only to a very slight extent upon the efficiency of the mechanism of expectoration under circumstances which are decidedly different.

The rate of disappearance of lipiodol from the lung under pathological conditions is interesting. Carlson, Wilson, Graham and I frequently found marked retardation of elimination from a normal lung in the presence of a paralyzed diaphragm. We were experimentally unable to confirm the teaching that artificial paralysis of the diaphragm provides a means of increasing the mechanical efficiency of cough and expectoration. The alleged facilitation of these two mechanisms following phrenicectomy is probably attributable to the influence of rest and relaxation of the lung upon pulmonary disease. Of equal significance, however, is the observation that even in the presence of a paralyzed diaphragm foreign bodies can be expelled from the bronchi of the lung on the side of the paralyzed diaphragm. A typical experiment along these lines will be described briefly. Two foreign bodies (lead shot) were inserted into each lower lobe through a bronchoscope, a right phrenicectomy having previously been performed. The animal was then made to cough whereupon one of the foreign bodies from the healthy side was "coughed over" to the lower lobe on the side of the paralyzed diaphragm. Further stimulation of the cough reflex resulted in the ejection of the remaining foreign body from the normal half of the chest and subsequently in the ejection of some of the foreign bodies from the lower lobe on the side of the paralyzed diaphragm into the trachea and stomach. From these and other experiments we concluded, as already noted elsewhere, that objects can be expelled from a normal lung even though the diaphragm on the same side is paralyzed.

D. H. Ballon and I in studies (1926) which at the suggestion of Doctor Pirie recorded inspiration and expiration on the same film showed that cough may spread injected oil deep into the lungs. The normal changes which facilitate the disappearance of lipiodol from the lungs can result in a radiological picture which in every respect resembles one attributed to the experimentally produced beneficial effects of an expectorant. Upon the action or upon the value of expectorants, about which so much has been written and so little said, I prefer to remain silent.

To return for a moment to the foreign body experiments to which reference has just been made, you may question the interpretation. Your own conclusions may be that foreign bodies roll out of bronchi more readily in the presence of a paralyzed diaphragm, and that neither cough nor expectoration need have played a part particularly since we were working with quadrupeds. Such a conclusion is acceptable to me as a possibility. And I would even go one step further. From personal observations and from bronchospirometric studies reported by Jacobaeus, I would suggest that secretion from a diseased lung or bronchus may not only spill over to the healthy contralateral lung but can also on occasions actually be coughed up and expectorated from and "by" the healthy lung. Let us recall at this point that all secretion which spills over, or oil which is injected into the bronchial tree, need not necessarily enter the lung proper. No reference has been made to muscle tonus. Obviously much that deals with it and postoperative complications has a bearing on our discussion.

SUMMARY

In summarizing I would say that it is agreed that phlegm and other secretions are discharged or expelled *ex pectore*. It is therefore permissible to speak of a mechanism of expectoration. It is also agreed that "excrementitious humours are expectorated by a cough" (G. Harvey morb. angl., 1672, *23*), further that the mechanism of expectoration may function without audible accompaniment of a cough. The bronchomotor mechanism is common to both cough and expectoration.

When I empirically interrupted the mechanism of expectoration by dividing it into two phases, the second phase you will recall starting at the point of beginning activity of the cough reflex, I did so for two reasons. These were on the one hand to emphasize that expectoration is a slow mechanism and on the other to draw particular attention to the adequacy and efficiency of the bronchomotor apparatus. It is appre-

ciated that expectoration is influenced by raising the intrapulmonic air pressure and then suddenly allowing the air to escape and carry with it any peccant matter which may be lying in the bronchial passages (Wall). Pressure changes, muscle tonus, posture, the ciliary and bronchomotor systems, etc. are all accepted as important teeth. They do not occlude. On the contrary, like carpentry cogs they act as tenons on the ends of beams, the one being received into a corresponding mortice on the surface of another. The resulting relatively smooth motion of the various cogs in the mechanism of expectoration may however be interrupted by disease. Examples have been given.

It is obvious that much information is needed upon many of the parts which I have put to work in the description of the mechanism of expectoration. When such information is available we will be provided with a more satisfying explanation than the one presented here.

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EXTRAPLEURAL PNEUMOTHORAX[1]

PAUL GEARY[2]

Intrapleural pneumothorax when satisfactory is generally considered the most direct and adequate treatment for the pulmonary cavitation of tuberculosis. Unfortunately, the pleural layers are often adherent over the diseased area, so that the introduction of air into the pleural cavity causes collapse of the good part of the lung and fails to induce the collapse in the area where it is needed. There has been much interest of late in a new form of pneumothorax, which circumvents the problem of pleural adhesion by the introduction of air outside of the parietal pleura rather than into the pleural cavity. This extrapleural space is created by operation and maintained the same as the space of regular artificial pneumothorax. It is not a new idea for, in 1910, Tuffier performed the operation and maintained the space with refills. There was, however, only occasional application of the procedure until Graf, of Germany, adopted it a few years ago as an alternative treatment in selected patients, upon whom he formerly would have performed extrapleural thoracoplasty.

The extrapleural space has frequently been considered as a possible solution to the problem of pulmonary collapse for tuberculosis. After creating the space by dissection, attempts have been made to maintain it by filling with muscle, fat, paraffin or other foreign bodies. Paraffin is the medium which has proved most practical. There were, however, a number of drawbacks to the operation which soon became evident. Without going into a lengthy discussion, it can be said that the most annoying complication was the development of a fistula between the cavity of the lung and the extrapleural space containing the paraffin. This usually resulted in the expectoration of the paraffin, infection of the space and an eventual thoracoplasty, often upon a patient who was

[1] A preliminary report on operations performed at the New Jersey State Sanatorium, Glen Gardner, New Jersey, Bonnie Burn Sanatorium, Scotch Plains, New Jersey, and the Roosevelt Hospital, Metuchen, New Jersey.

[2] 909 Park Avenue, Plainfield, New Jersey.

not a fit subject for it. For numerous reasons, it was necessary to limit the size of the paraffin plomb, with the result that the pulmonary collapse was inadequate and patients were left with open cavities, positive sputum and in a condition similar to that prior to operative intervention.

Using air as a medium may, at first thought, simulate the paraffin plombage quite closely, but actually it is very different, because air is more pliable, the quantity can be altered and it is less irritating than the more solid medium. We feel that the procedure is akin to intrapleural pneumothorax, for it is maintained in the same manner and exposed to similar complications. In any comparison of the advantages and disadvantages of intrapleural and extrapleural pneumothorax, it must be borne in mind that, so far, the extrapleural pneumothorax is used only in cases where the intrapleural pneumothorax has failed because of adhesions.

There is a fairly well defined group of individuals whose tuberculosis cannot be controlled by intrapleural pneumothorax, and who, for one reason or another, are not acceptable for thoracoplasty. It is our impression that the paraffin plombage, which at one time we adopted, has failed to justify its use in this group. We feel now that extrapleural pneumothorax is more desirable and a worth while addition to the surgical treatment of pulmonary tuberculosis.

Bearing in mind the unnatural location of the extrapleural air space and the difference in its lining from that of the endothelium of the pleura, it seems hard to believe, after our observations to date, that the insertion of the pneumothorax needle into the extrapleural space can set up a series of hazards which are far more malicious than those of intrapleural pneumothorax. This, however, appears to be the common belief. In support of this stand are cited the dangers of infection, fistula and haemorrhage, as well as the possibility that the patient may eventually need a thoracoplasty to relieve the dead space of extrapleural pneumothorax.

We believe that when intrapleural pneumothorax is inaugurated the patient faces just as much danger of infection, and many of the unsuccessful ones face thoracoplasty. Furthermore, massive effusion followed by atelectasis of the good part of the lung can occur in intrapleural pneumothorax, as well as massive spontaneous pneumothorax with its complications. In this series of cases, where the extrapleural space was established and maintained fifty-three times on fifty-one patients, we have had but one troublesome haemorrhage, no fistulae, either bronchial or cutaneous, nor atelectasis on the operative side.

It is true that we are dealing with an experimental procedure with known immediate complications and unknown complications which may develope in the future. It, therefore, behooves us to go cautiously and follow the advice of those who are best entitled to an opinion on the subject. The universal advice is a warning against doing the operation on those patients who are acceptable for thoracoplasty.

We have all seen the benefits of thoracoplasty; the procedure is tried and true, and it would be folly to abandon it for another which is in the trial phase. This will make need for so-called "sales resistance" in dealing with our patients, because all of them naturally prefer the removal of a part of a rib to the sacrifice of six or seven. In addition, many get the impression that anything that is new is better. We should not lose sight of the fact that after a thoracoplasty is performed the operative procedure is over, while the operation itself is only the beginning of extrapleural pneumothorax treatment.

It is poor surgery to leave a dead space in the body. This is our greatest apprehension. We do not know what will happen to it and therefore must speculate. We would judge, on the basis of our present experience, that pulmonary tissue underlying an extrapleural pneumothorax, which has been stabilized for a year, would have great difficulty reëxpanding, due to the fibrous capsule of the extrapleural pneumothorax space. It may be possible that if such an attempt were made the space would fill with fluid and eventually organize. It also seems that, if the space were stabilized the first year, the eventual outcome would probably be indefinite continuance of the refills or thoracoplasty. However, the fibrous capsule does not become nearly as thick and resistant as our experience with paraffin plombage had led us to believe it would.

Since we adopted extrapleural pneumothorax early in June, 1938, fifty-five operations have been performed on fifty-three patients. On two occasions, it was impossible to effect a cleavage between the lung and chest wall. One patient had the operation on each side and another had two operations on the same side.

INDICATIONS

1. Bilateral disease where intrapleural pneumothorax is impossible or unsatisfactory and thoracoplasty contraindicated.

2. Contralateral thoracoplasty. The operation is more selective than thoracoplasty and will not produce as much dyspnoea as would bilateral thoracoplasty.

3. Asthma or any condition where there is a low vital capacity.

4. Childhood and early adolescence. Children, adolescents and young adults are greatly disfigured by thoracoplasty. Extrapleural pneumothorax can be used until full growth is reached and then converted to thoracoplasty if necessary.

5. Acute progressive activity, where intrapleural pneumothorax is impossible. Thoracoplasty is often too hazardous in this group because of fever and toxicity.

6. Haemorrhage; patients with more or less continual bleeding are more liable to have a contralateral spread after thoracoplasty.

7. Basilar cavitation; operation may obviate a three-stage thoracoplasty.

ANAESTHESIA

In the uncomplicated case, we have little preference for either local or general anaesthesia. Both are satisfactory. Local alone was used twenty-eight times, general alone twenty-six times and a combination of both on one occasion. It seems that in the presence of a large amount of sputum, local anaesthesia is preferable, thereby enabling the sputum to be expectorated if it is squeezed from the lung during its collapse. On the other hand, general anaesthesia is necessary in a large group of patients to facilitate the division of adhesions in the mediastinal region. If the operation is being done under local, manipulation of adhesions in the mediastinal area often causes cough and violent respiratory movements, which tend to obscure the field.

Cyclopropane has been the anaesthetic of choice where we have used inhalation. With local, it has been our custom to use 1 per cent procaine. The skin and muscles are infiltrated. The intercostal nerves accessible from the incision are blocked. The periosteum of the rib to be removed is infiltrated. In the extrapleural cavity the same solution of procaine has proved satisfactory and is used topically by pouring it into the space as the operation progresses.

TECHNIQUE

In our hands, an incision parallel to the spinal border of the scapula has proved the most satisfactory (figure 1A). It is very similar to the regular thoracoplasty incision but not as extensive. In thin patients we occasionally employ an oblique incision over the fourth rib. This incision has the advantage of being smaller and less traumatic, because

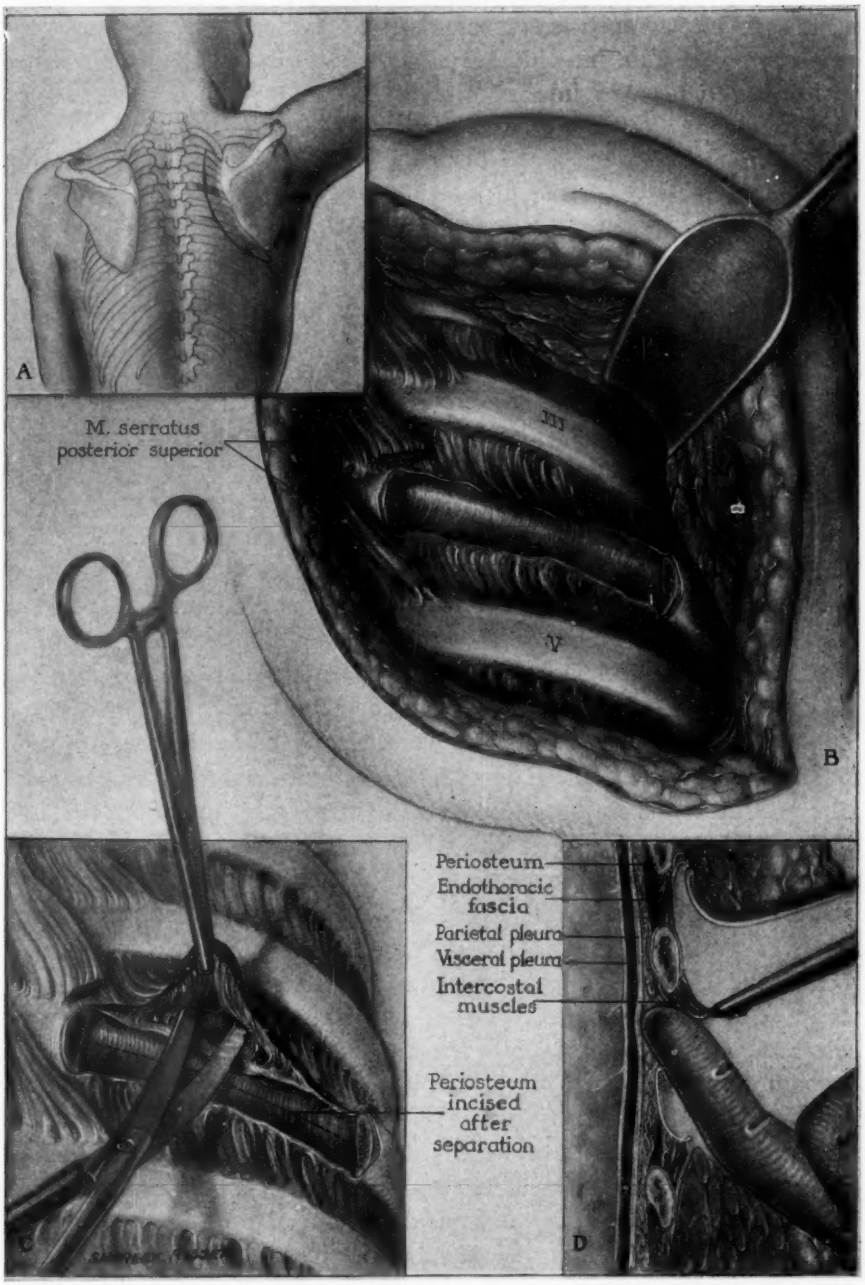


FIG. 1. A: Incision. B: A part of the fourth rib has been subperiosteally resected. C: Approach to the extrapleural region through the intercostal muscles. D: Creation of the extrapleural space is begun with the finger.

all the muscles except the trapezius can be divided by blunt dissection. In all but very thin individuals, it has the disadvantage of interfering with infiltration of the intercostal nerves as well as tending to obstruct the cleavage in the more remote portions of the chest.

The muscles are cut in the line of the incision (figure 1B). About four inches of the fourth or fifth ribs are resected periosteally, starting from a point one-half inch medial to the angle and going laterally. About four centimetres of the intercostal nerve are removed from the resected rib bed.

It seems to us that the plane of cleavage is most easily and safely reached by avoiding the periosteum. It has, therefore, been our practice to grasp the group of intercostal muscles presenting above the periosteum and applying some tension. Blunt pointed scissors are inserted under the muscle and the blades separated (figure 1C). This manoeuvre brings the correct plane of cleavage into view and the dissection is continued with the finger (figure 1D) as far as it can conveniently reach. A scissors is then used to divide the periosteal bed in each direction. From this point, the dissection is continued with gauze on the end of an artery clamp. A hand light or illuminated retractor is used later to light the field. An occasional adhesion has to be cut, but the greater part of the dissection is done bluntly.

For upper lobe disease, we dissect anteriorly as far as the third or fourth rib, posteriorly to the seventh or eighth rib, downward toward the hilum as far as the aorta on the left and the azygos vein on the right.

There is always oozing in the region of the costal cartilages in the spinal gutter and near the mediastinum. The bleeding is controlled by gauze packing. Where this is not successful, ligatures or metal clips are used. We feel that diathermy coagulation might cause a slough with secondary haemorrhage or fistula of the lung and have not used it. To secure an unusual bleeder, a rib spreader is applied, which allows a better view and almost doubles the amount of room in the chest wall through which to work. When the pleurolysis is finished and the bleeding is controlled, the cavity is irrigated with saline solution until all the clots are removed and the return is clear. In the beginning, we left a few hundred cc. of the solution in the wound to prevent expansion. This was soon found unnecessary and was discontinued.

The intercostal muscles and periosteum on each side of the incision are sutured together with interrupted or continuous chromic catgut (figure 2A). Whatever leaks exist, after this closure, are soon filled with

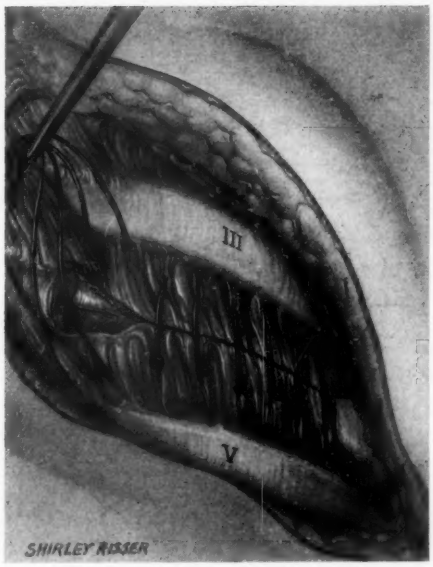


FIG. 2A

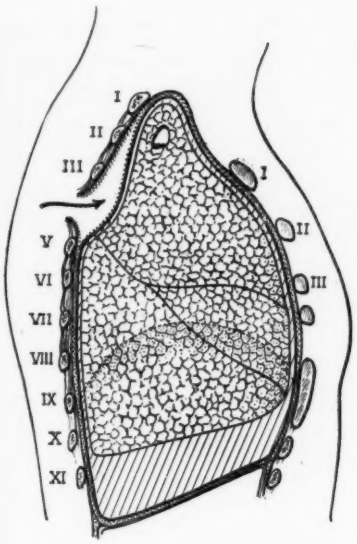


FIG. 2B

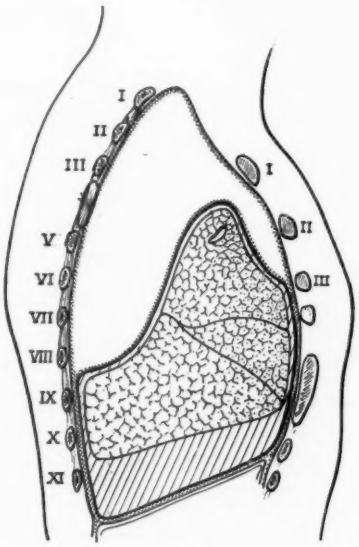


FIG. 2C

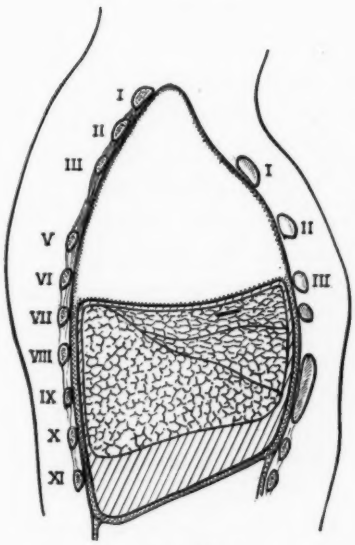


FIG. 2D

FIG. 2. A: Method of closure after pleurolysis and creation of the extrapleural space. B: The parietal pleura and underlying plumonary tissue being separated from the chest wall. C: Appearance of the lung and extrapleural space immediately after the operation. D: After pneumothorax therapy for several months changes are noted in the peripheral attachments and the shape of the lung.

serum and it is unnecessary to make closure of the costo-intercostal layer absolutely air-tight. (The amount of emphysema which follows is limited and has caused no trouble.)

Ordinarily, it is unnecessary to inject any air into the extrapleural space during the first twenty-four hours. Our one exception to this rule has been in those cases which have a tendency to ooze. By keeping the pressure on the positive side, the bleeding tendency is more liable to be controlled than if it were allowed to remain negative or atmospheric.

It is necessary to make the dissection ample, because shrinking takes place postoperatively when the exudate is absorbed (figures 2C and 2D). This shrinkage is proportionally much greater in a small space, and probably was an important factor in the obliteration encountered in earlier operations. On the other hand, we feel that extensive dissection may be more dangerous for reasons mentioned elsewhere, namely, massive tuberculization or blood-stream infection, due to sudden closure of a tuberculous cavity, or irritation of cerebral centres, due to the stimulation of the thoracic sympathetic chain.

It has been noted on numerous occasions that the extrapleural space obtained after refills is greater than that created at operation. This fact was also observed by Sellors, who attributes the additional stripping to the pressure of the air in the space.

We have transfused many of our patients immediately after the operation, to replace the blood loss. The sitting position, as recommended by Roberts and also by Overholt and Tubbs, has not been used. It is our thought that the serosanguineous fluid, which collects, gravitates to the area of the incision and is instrumental in limiting the emphysema.

A refill is given the day following operation. Enough air is given to bring the pressure from the negative side to mean or slightly positive, which usually is about 150 cc. The second day, the patient is fluoroscoped or X-rayed and the amount of the refill to be given is judged by the extent of the collapse. The average fill on the second day is about 100 cc. Frequently, positive pressures are required but difficulty with maintaining the collapse is the exception rather than the rule. The patients, in whom it is difficult to maintain the collapse, are those with a low vital capacity from extensive disease, asthma or contralateral pneumothorax. Frequently it is imperative to remove some air, temporarily, from a contralateral pneumothorax during the early postoperative days. In the beginning, it is better to fluoroscope often, to make sure that the collapse is satisfactory. As time progresses, the refills are smaller and

required less frequently. It is probable that in the earlier postoperative period the amount of the refills could be judged fairly accurately by interpretation of the manometric readings alone. This statement, of course, presupposes that there is not an unusual amount of emphysema of the tissues.

COMPLICATIONS

We have had five infections of the extrapleural space, two pyogenic and three tuberculous.

One patient (case 5) developed a staphylococcic infection of the space prior to a fatal termination, presumably from other causes.

The second patient (case 19) developed a tuberculous infection of the extrapleural space. It was noted postoperatively that she had a combination extrapleural and intrapleural pneumothorax, although we were aware of no tear in the pleura at the time of operation. After two irrigations with an antiseptic solution, the fluid became negative for tubercle bacilli. Aspiration is still required about every three weeks, but the clinical condition is good.

Another patient (case 20) has developed a tuberculous infection of the extrapleural space, four and a half months after operation. It will be noted that he has a combination extrapleural and intrapleural pneumothorax and is referred to elsewhere in this article.

In the fourth, a patient with a positive Wassermann (case 21), infection developed in the space. He had a combined extrapleural and intrapleural pneumothorax, as a result of the parietal pleura being accidently torn at operation. Neither tubercle bacilli nor pyogenic organisms were recovered on numerous examinations, so the presumption is that it is tuberculous. The communication between the extrapleural and intrapleural space has closed, with full expansion of the lower lobe. With the subsiding of the infection, marked clinical improvement has taken place. At present, watery fluid slowly accumulates and is aspirated when necessary.

One pyogenic infection involved the wound as well as the extrapleural space (case 35). *Staphylococcus aureus* was recovered from both areas. The wound has been entirely healed and the temperature normal for one month. The infection of the extrapleural space has subsided both according to clinical and bacteriological examination. We are, however, continuing the aspirations and instillations for a while longer.

The fact that all three of our tuberculous infections of the space oc-

curred in patients in whom the parietal pleura was accidently torn during the procedure would lead us to believe that this is more than a coincidence.

Portions of two ribs were removed in one patient (case 17) to facilitate a very difficult pleurolysis. The patient's lung was hard and inelastic, showing little tendency to collapse. An interesting thing about her convalescence was the fact that she developed a postoperative bulging at the point where the sections of ribs were removed. The defect was strapped with adhesive for a few months until stiffening took place.

One of our early cases (case 3), whose dissection went only to the second anterior and sixth posterior ribs, is obliterating because of inadequate dissection. Another (case 23), in whom the pleura was torn, developed a large effusion into the combined space postoperatively. Due to a contralateral thoracoplasty she was dyspnoeic and unable to tolerate adequate refills.

Serosanguineous fluid has developed in all the cases. Aspiration was performed in thirty-six. In some it was done because of fever reaction, extensiveness of the effusion or discomfort in the chest. In others it was done because we thought it was a good thing to keep the chest dry. The latter practice has been discontinued.

We had one haemorrhage into the extrapleural space (case 51) which caused a severe reaction but responded well to transfusion and aspiration.

Following operation, another patient (case 28) developed a contralateral tuberculous allergic reaction. He was ill and showed a haziness in the contralateral lung. In two weeks the patient recovered with complete clearing of the X-ray picture. Since then his course has been satisfactory.

There have been four deaths. The first (case 5) was in a sixty-two year old male with silico-tuberculosis, accompanied by the usual dyspnoea. He had bilateral disease, with extensive fibrosis. It was impossible to free a giant cavity at the right apex, so the operation was abandoned. He died of general toxicity ten days later. At autopsy the extrapleural space was surrounded by a dense fibrous capsule about 2 mm. thick. The tuberculous cavity was thick walled and intimately attached in the region of the bodies of the vertebrae. We know now that in spite of this patient's shortcomings as an operative risk his selection was ill advised. It is generally agreed that a giant thick-walled cavity at the apex should not be treated by extrapleural pneumothorax, because the chances of cavity closure are slim. Furthermore, these cavities

frequently receive their nourishment from a parietal adhesion and if this source of blood supply is cut off a slough may form, which will be followed by bronchial fistula and infection.

The second death (case 26) occurred in a patient with bilateral disease. His progress was complicated by emphysema, laryngitis, contralateral pneumothorax and poor general condition. He expired on the tenth postoperative day, from a spread of the tuberculous infection to the other lung.

The third death (case 30) was unexpected. A twenty-five year old female developed a bronchopneumonia on the second postoperative day, from which she died on the fifth day. The diagnosis was confirmed at autopsy; tubercle bacilli were present in a cavity in the deflated lung.

The fourth death (case 48) was in a patient with a large, thin-walled cavity at the apex of the lower lobe. His immediate postoperative period was usual until the following day, when his temperature rose to 107°F. A roentgenogram taken at that time showed an extensive dissection to the eleventh posterior rib. There was no dyspnoea and no fluid in the extrapleural space. The manometric readings were -2 $+3$; 950 cc. of air were removed, leaving the pressure at -1 -5. The next afternoon he had a chill, at which time his temperature rose to 109°F., when cyanosis and dyspnoea developed, which was followed a few hours later by death. No autopsy was obtained. A blood culture taken on the second postoperative day showed a luxuriant growth of *streptococcus viridans* in twenty-four hours. Nothing in the history or physical examination showed evidence of previous endocarditis. It has been suggested that the sudden closure of the thin-walled cavity was instrumental in causing the secondary organism to traverse the lymph spaces of the lung and enter the blood-stream in sufficient quantities to establish an overwhelming infection.

Mediastinal emphysema developed in one patient, causing difficulty in swallowing. This symptom was present until the fourth day, when no further discomfort was noted. Three patients developed contralateral spread after the operation and two developed late contralateral effusion.

We feel that violent reactions which follow the extrapleural pneumothorax operation are liable to occur if the dissection is too extensive and that they are due to irritation of the cerebral centres by stimulation of the sympathetic chain, or massive tuberculinization by sudden closure of cavities.

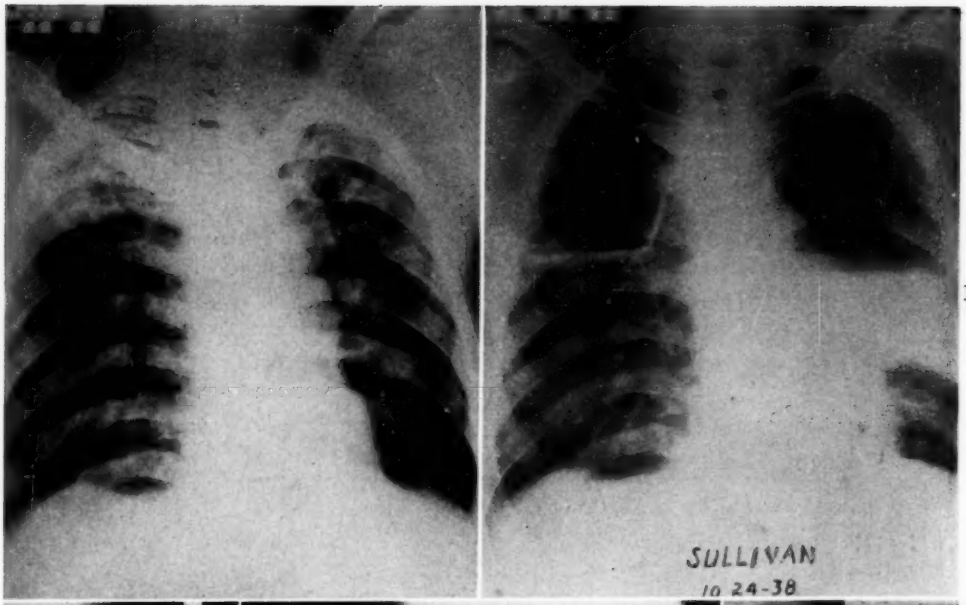
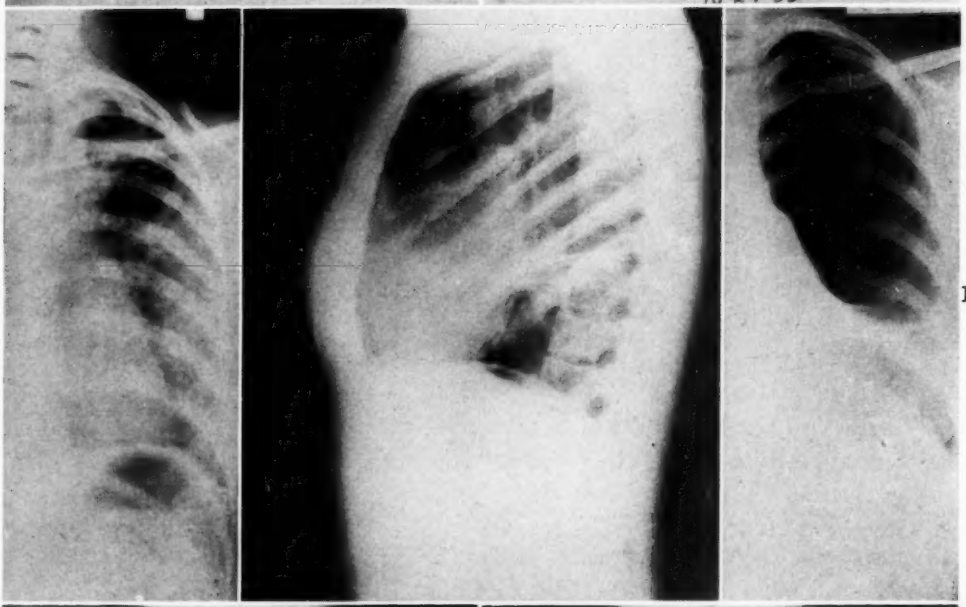


FIG. 3A

FIG. 3B



FIGS. 4A & 4B

FIG. 4C

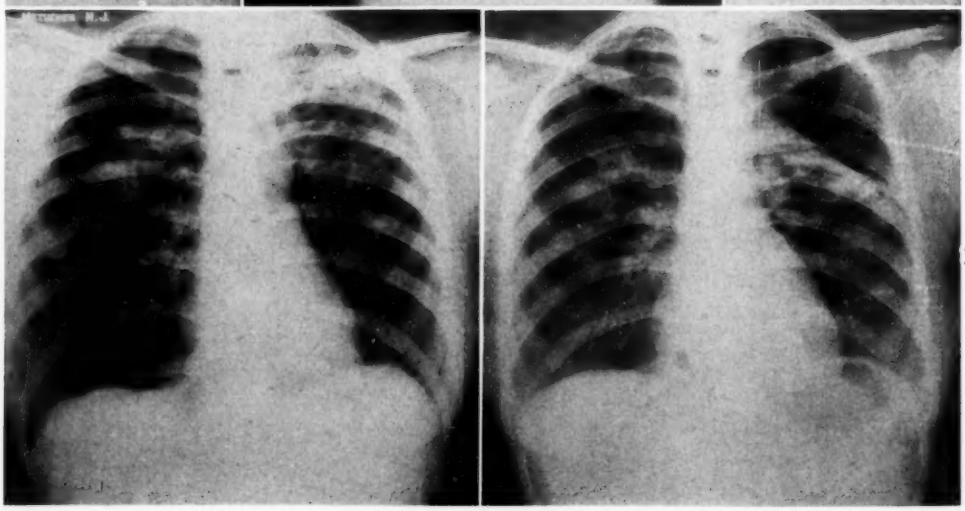


FIG. 5A

FIG. 5B

We had one patient (case 1) who had the operation performed on both sides. He had a fibrocavernous lesion at each apex. His sputum was always positive until his second operation, since then it has been negative. There has been general clinical improvement with normal temperature and gain in weight.

Two of our patients (cases 11 and 29) had basilar lesions with cavitation in the lower lobe. A third had a cavity at the base of the middle lobe.

Although Freedlander has recently described two patients in whom lower stage thoracoplasty alone was done successfully for basilar lesion, most of the thoracoplasties to-day are done from above downward. By the usual method, at least three stages would be required to close a basilar lesion.

On both patients with basilar cavities a splendid result was obtained by performing a pleurolysis at the base rather than at the apex (figures 7A and 7B). In one, the seventh rib was resected and in the other, the eighth. As the muscular coverings are less and the protection of the scapula is absent from this region, it is plausible to suspect that emphysema would be more troublesome. This, however, was not so. There is general improvement in both. In one (case 11) the sputum turned positive after four months, and a cavity was discovered in the apex of the operated lung, so a second operation was done which collapsed the upper lobe.

During the process of dissection in one patient (case 20), in whom the pleurolysis was extremely difficult, the parietal pleura was torn in several

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FIGS. 3A & 3B. Case 1. A male, forty years of age, with bilateral apical cavitation. Onset was in 1937. There was no free space for intrapleural pneumothorax on either side. His first operation was in June, 1938, on the right side; the second in August, on the left. Since the second operation, his sputum has been persistently negative, his temperature has been normal and he has gained fifteen pounds.

FIGS. 4A, 4B & 4C. Case 2. A girl, eighteen years of age, with rheumatic heart disease. She was admitted in April, 1937, and has had a very stormy course since then, due to alarming haemorrhages, which were followed by spread and systemic reaction. Never in a safe condition for thoracoplasty, an extrapleural pneumothorax was done in June. Since then, she has not bled, her sputum has been negative and she has been on exercise since September. There is a lateral as well as a posteroanterior view, showing the extent of the collapse six months after operation.

FIGS. 5A & 5B. Case 6. A woman, twenty-six years of age, with bilateral involvement. The right side is controlled by intrapleural pneumothorax. No free space was found on the left, so an extrapleural pneumothorax was done on July 5, 1938. This was followed by general clinical improvement and persistently negative sputum.

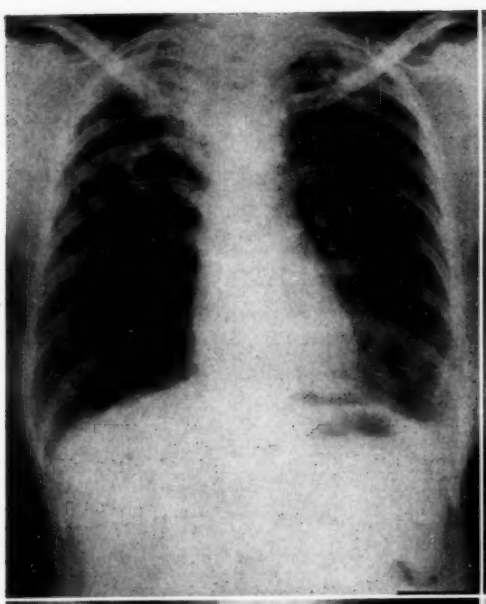

FIG. 6A

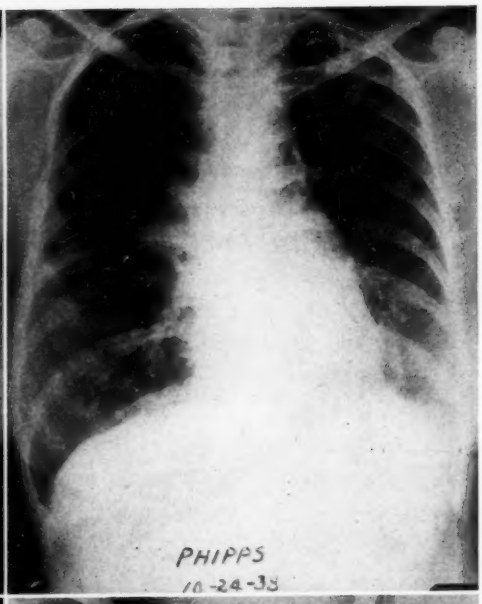

FIG. 6B

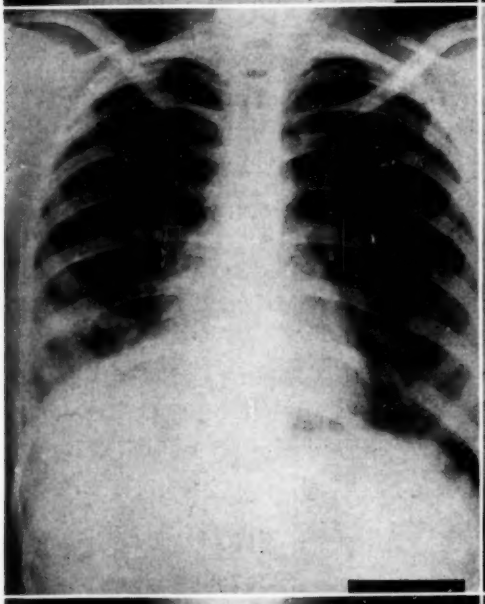

FIG. 7A

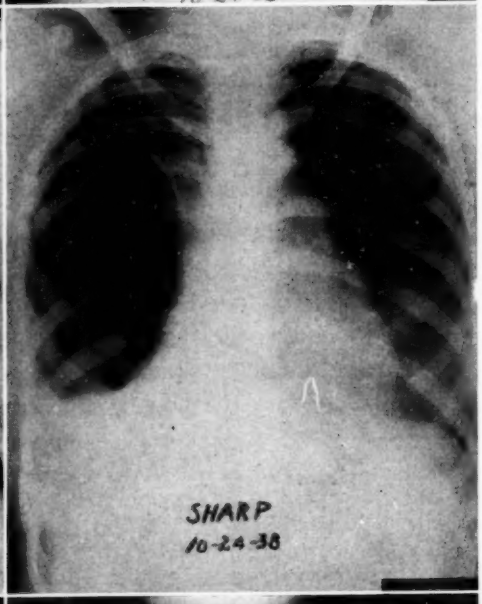

FIG. 7B

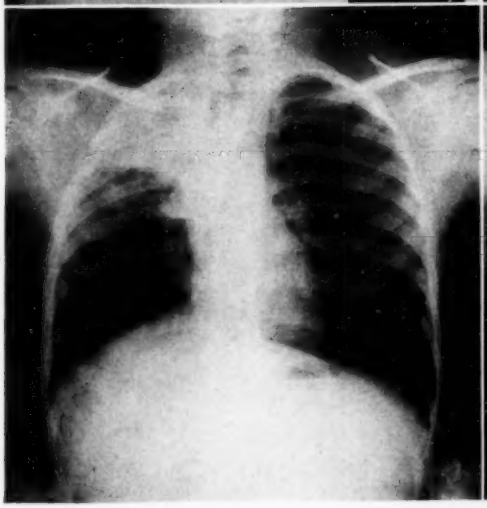

FIG. 8A

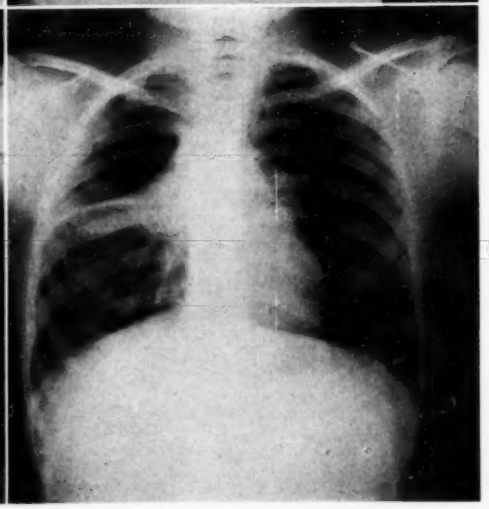

FIG. 8B

places. In order to prevent any pocketing in either cavity, the entire parietal pleura in the line of the rents was sectioned, thereby making the two cavities into one. He was operated upon four and a half months ago and did well until last week, when a tuberculous effusion developed on his operative side.

FIG. 6B

Brock has combined an extrapleural and intrapleural pneumothorax in seven of his first fifty cases and is very enthusiastic about the benefits derived. He believes that it should preferably be done later, as a separate procedure, rather than at the time of the original operation.

It was our impression that the dissections which were the most difficult were least liable to be followed by satisfactory compression. In our series, this assumption was shown to be false, because at this writing the cases which were more difficult to dissect have shown a greater percentage of cavity closure. We, of course, believe this to be coincidence, because it is the hard, inelastic lung which is most difficult to free and which naturally would be expected to respond most poorly to compression.

In the cases with adequate dissection and enough functioning lung tissue, we have, so far, noticed no more tendency to reëxpand than in intrapleural pneumothorax. Roberts makes a similar observation in cases which are more than a year old. With low vital capacity there is a definite tendency to reëxpand and although we have not employed oil filling to prevent expansion, I feel that a few of the cases will soon require it.

FIG. 7B

Some of our patients have had trouble raising the sputum during the first twenty-four to forty-eight hours. After this initial period, the cough is relieved and usually less effort is required than before operation.

At this time our impressions of the operation are favorable. In occasional cases it can accomplish dramatic results, often in a short space of time, where no other method at our disposal could be employed.

FIGS. 6A & 6B. Case 16. A woman, fifty years of age, with onset in 1933. There was no free space on the right, and a suspicion of a cavity on the left. An extrapleural pneumothorax was done on August 23, 1938. Since then her sputum has been negative, her cough has decreased and she is better generally. A marked improvement noted on the left side.

FIGS. 7A & 7B. Case 29. A girl, eighteen years of age, with a cavity in the right base. Phrenic interruption was done in December, 1937, without improvement. A basilar operation, done on September 28, 1938, was followed by clinical improvement and reduction of the sputum, which has been persistently negative.

FIGS. 8A & 8B. Case 34. A boy, twelve years of age, with a fibrocavernous lesion at the right apex. There was no free space, so an extrapleural pneumothorax was done on October 20, 1938. He has gained weight and shown general clinical improvement. For the last few months there has been no cough or expectoration.

FIG. 8B

We do not feel that it should be substituted for extrapleural thoracoplasty in favorable cases where a satisfactory result would be expected. It will probably find a definite place in the treatment of unstable and toxic patients, who apparently tolerate the operation very well. There will be considerable difficulty in maintaining the space for a long period in all patients whose vital capacity has been greatly lowered by contralateral disease or compression therapy. It is possible that the procedure may be used more freely in the future for various reasons, the most important of which are the freedom from the deformity which is associated with thoracoplasty and the need of only one operation. Directly opposed to this reasoning is the fact that thoracoplasty often completes the operative treatment, while extrapleural pneumothorax is only the beginning. However, it seems conceivable that the operation may someday be used instead of thoracoplasty to collapse a small area of diseased pulmonary tissue, with the idea of allowing reëxpansion of the extrapleural pneumothorax after it is estimated that healing has occurred. An encouraging number of sputum conversions have been obtained but the observation period is much too short to report these in detail.

SUMMARY

1. Fifty-five operations were performed upon fifty-three patients; no plane of cleavage was found in two, forty-nine had a single operation, one patient had the operation on each side and another had two operations on the same side.

2. The procedure is not considered a substitute for extrapleural thoracoplasty but rather an addition to the other forms of surgical treatment of pulmonary tuberculosis.

3. It is used only in patients where intrapleural pneumothorax was impossible or inadequate. In addition, the indications for the operation, the type and effect of the compression and the nature of the complications are akin to intrapleural pneumothorax.

4. The operation is well tolerated by patients with fever and the other usual signs of toxicity. On the other hand, marked reactions after operation have been observed when not expected.

5. Results of the operation to date are encouraging.

6. Early complications have been encountered but our greatest concern, in the future, will be with the management of the extrapleural space.

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PHRENIC NERVE INTERRUPTION[1]

Its Place in the Collapse Therapy Program of Pulmonary Tuberculosis

J. W. CUTLER

Phrenic nerve interruption continues to be one of the most controversial subjects in the therapy of pulmonary tuberculosis. Claims are contradictory and confusing, in spite of published reports covering thousands of operations.

Nehil and Alexander (1) observed closure of cavity in 38 per cent of 215 cases when phrenic nerve paralysis was used as the sole collapse measure. Alexander has expressed a favorable opinion in his recent book on *The Collapse Therapy of Pulmonary Tuberculosis* (2).

Edwards and Stevens (3) obtained closure of cavities in 19.4 per cent in one series of 180 patients on whom phrenicectomy was used as the sole form of collapse therapy. Potter, Berry and Bortone (4), in a recent study of 68 cases in which the operation was used as an independent procedure, found, in retrospect, that only 38 of these patients were suitable for the operation but that, in this group, closure of cavity occurred in 47 per cent. Aufses (5), in an exhaustive review of the literature on phrenic nerve operations, collected the published results of 78 authors with reports on 7,435 operations performed as an independent procedure, and found "cures" reported in 1,734 cases, or 23.3 per cent.

On the other hand, Coryllos (6) considered phrenic nerve paralysis alone of little help in the treatment of pulmonary tuberculosis. According to him, it is "not efficient, not without danger, and causes a loss of precious time." He also cited Sauerbruch in Germany, Bernard in France, Dumont and Conbresier in Belgium, Kan in Russia and Matz of the United States Veterans Bureau as among others equally skeptical about the efficiency of phrenicectomy. Ernst (7) of Leipzig is convinced that artificial paralysis of the diaphragm alone seldom effects a cure in unilateral tuberculosis. He reports 15 patients, a little more than 8 per cent, as cured and able to work, out of a total of 185 in whom phrenic exairesis alone was performed. Lambert (8) has repeatedly emphasized

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that a great many operations have been performed which have not resulted in any clinical benefit to the patient.

A wide divergence of opinion is thus evident. It is generally recognized that this divergence is in good part explained by the type of patient subjected to the operation. Many of the almost phenomenally good results attributed to the phrenic nerve operation are in relatively early cases, and they would undoubtedly have been obtained from bed-rest alone. On the other hand, phrenic nerve interruption in far advanced

TABLE 1

Summary of 122 consecutive phrenic nerve interruptions for pulmonary tuberculosis, with reason for operation

REASON FOR OPERATION	NUMBER OF OPERATIONS	PER CENT
1: As sole form of collapse therapy to "cure" tuberculosis:		
(a) When pneumothorax could not be instituted because of adherent pleura	67*	54.9
(b) In conjunction with contralateral pneumothorax as an alternative to simultaneous bilateral pneumothorax	39	31.9
2: As an adjunct to other collapse measures and in the treatment of certain complications:		
(a) To relieve cough	5	4.1
(b) To obliterate an empyema cavity	3	2.5
(c) To control haemoptysis	2	1.6
(d) To prevent relapse after pneumothorax had been discontinued.	2	1.6
(e) To relax adhesions (ineffective pneumothorax)	2	1.6
(f) To abolish a spontaneous pneumothorax	1	0.9
(g) To close a bronchopleural fistula	1	0.9
Total	122	100.0

* Five operations were performed at a time when the tuberculosis was in the process of spontaneous improvement. Although the operation probably played some part in the ultimate good result, these patients are not included in the statistical analysis of results.

disease and in the presence of large, thick-walled cavities can hardly be expected to produce many successes.

Although the indications for the operation have been narrowed, in conformity with accumulated experience, and limited for the most part to patients with small or moderate-sized cavities, the value of the operation remains far from settled and needs painstaking study and elucidation.

The likelihood to-day is not so much that too many phrenic nerve operations will be performed, or that they will be undertaken in an indiscriminate manner, but that the operation will be discarded.

In the following pages a review is presented of the results of phrenic nerve surgery in a consecutive series of 122 private patients under care for pulmonary tuberculosis for varying periods during the past nine years, and upon whom one or another type of phrenic nerve interruption was performed. In 106 patients the operation was carried out as an independent collapse measure. In the remaining 16 tuberculous patients the operation was employed, for a variety of reasons, in a supplementary capacity (table 1).

These patients are believed to represent a fair cross-section of the type of tuberculous patient in whom phrenic nerve surgery has been used. Many stages and varieties of tuberculosis are represented, from early, flocculent infiltration to far advanced disease involving one or both lungs. I know the great majority of these patients intimately and have kept accurate and detailed notes with repeated fluoroscopic and X-ray studies. All patients were white adults. Fifty-seven were males and 64 females. In 60 the operation was on the left side and in 62 on the right. In 65 the phrenic nerve interruption was temporary and in 57 it was permanent. The intelligence, coöperation and morale of these patients were on a higher plane than one usually encounters in clinic patients. These are points worth stressing, for, in a sense, by limiting the study to such a selected group the results should in a way represent the more favorable side of phrenic nerve paralysis.

CRITERIA FOR EVALUATION OF RESULTS

In evaluating the results of the operation, inherent difficulties arise which complicate a purely objective study. When phrenic nerve interruption is performed shortly after the diagnosis is made, the possibility remains that the resulting recovery in some instances might have taken place without the operation, on a simple regimen of diet and rest, particularly since bed-rest for a period of at least six months was part of the postoperative routine. The value of the operation in each case should, therefore, be appraised in a critical manner and on the basis of all associated factors.

In this series no credit is given the operation in those instances when there was definite X-ray evidence of a tendency to spontaneous healing at the time the operation was carried out (5 cases), even though it was felt that phrenic nerve interruption may have played a part in the rapidity of improvement. The great majority of patients whose postoperative course is made the basis of this study were making no noticeable progress at the time when the phrenic nerve interruption was undertaken.

On the other hand, it is reasonable to suggest that patients with lesions shown by experience as rarely responsive to phrenic nerve interruption should also be excluded from the general evaluation, but considered as a separate group. During the years of enthusiasm many patients were subjected to operation who, it is seen in retrospect, had no chance to benefit from it and should not have been subjected to it. In all likelihood, patients with similar lesions would be refused operation to-day as apparently unsuitable.

It should also become clear that an impartial evaluation of the operation should be based primarily on the changes that follow in the lung under consideration and not necessarily upon the ultimate fate of the patient. This suggestion is based upon the many clinical observations that the two lungs often behave differently in the same individual, and that the response of each to treatment will vary with the type and character of the collapse measure employed. Indeed, new infiltration or progressive and even fatal disease may be observed in the contralateral lung months and even years after the phrenic nerve operation, with healing in the lung subjected to phrenic nerve paralysis. Or an intervening complication, such as tuberculous meningitis or contralateral spontaneous pneumothorax, may occur and kill the patient. Phrenic nerve paralysis may have nothing whatever to do with such developments.

It is also reasonable to suggest that the evaluation be based primarily on comparative X-ray findings. All terms used in this study, such as "improved" or "cleared," are based on X-ray evidence.

The time element, following operation, is of extreme importance. There is general agreement that the good results of phrenic nerve interruption become evident within the first three to six months after operation, or not at all. At least the most striking phases of recovery occur during that time. In speaking, therefore, of immediate results reference is made to a three- to six-month period following operation, during which time bed-rest is an essential feature. The late results of phrenic nerve interruption, on the other hand, are a little more difficult to define, as relapses may occur at any time in the future life of the tuberculous patient. A three- to five-year postoperative interval, as a basis for late results, is not unreasonable. The average period of observation of the 122 patients in this study was 25.9 months, with more than 50 per cent observed for periods from two to eight years. No operations are included that were performed after March 1, 1938.

If agreement could be secured on such criteria as those indicated above, and the evaluation of phrenic nerve interruption conducted within the limits implied, it would make possible an orderly appraisal of the operation which should go far to eliminate the present confusion with its contradictory conclusions by equally competent and sincere observers.

With the above considerations in mind, the evaluation of phrenic nerve interruption will be discussed under four main headings, as follows: (*1*) the value of the operation as an independent collapse measure, with a brief analysis of phrenic nerve interruption as an alternative to artificial pneumothorax or thoracoplasty; (*2*) the value of the operation as an adjunct to other collapse measures, and in the treatment of certain complications of pneumothorax therapy; (*3*) complications of the operation; and (*4*) temporary as contrasted with permanent phrenic nerve interruption, and their corresponding indications and contraindications.

PHRENIC NERVE INTERRUPTION AS AN INDEPENDENT COLLAPSE MEASURE AND AS AN ALTERNATIVE TO ARTIFICIAL PNEUMOTHORAX OR THORACOPLASTY

Phrenic nerve interruption was used as an independent procedure to close cavities and control disease in 106 patients under two different conditions (table 1): (*a*) in 67 cases it was carried out when pneumothorax could not be established because of a widely adherent pleura; (*b*) in 39 cases it was employed in conjunction with a contralateral pneumothroax, as an alternative to bilateral pneumothrax. Generally speaking the disease in this group was less severe, less extensive and apparently less active then was the case in group *a*.

Phrenic nerve interruption was not used in place of pneumothorax in unilateral disease when a successful pneumothorax could be established.

As mentioned previously, in 5 cases the operation was carried out, as seen in retrospect, at a time when the disease was apparently in spontaneous improvement and, although the operation may have played a part in the rapidity with which the desired result was obtained, these 5 cases, in keeping with the criteria enumerated above, are eliminated from the analysis, leaving 101 cases for study. Also in keeping with the above criteria, the cases are classified, in retrospect, as "apparently suitable" and "unsuitable," and the results in each group studied as separate problems.

Results in Unsuitable Cases

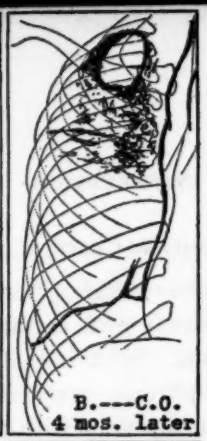
One of the most striking observations emerging from a study of post-operative results is the fact that patients with certain types of lesions are seldom benefited by the operation. Such lesions may be referred to, in retrospect, as unsuitable for phrenic nerve interruption. The variety of unsuitable lesions will naturally vary with the liberality with which phrenic nerve interruption has been performed. In this series failure was the rule in the case of the following lesions:

(*1*) *Apical cavities 3 or more cm. in diameter:* There is general agreement that the operation is useless in the attempt to close apical cavities in which the apex has become more or less excavated and adherent to the thoracic wall. Of 20 patients in this series with a cavity at the apex, 3 or more cm. in diameter (3.3 × 3 to 9 × 5.5 cm.), with or without a thick wall, as determined by X-ray, not one was closed or even materially reduced in size (C. O., figure 1). Five patients did show improvement following the phrenic nerve interruption, but the improvement was largely in the surrounding infiltration and not in the size and character of the cavity.

(*2*) *Dense fibrotic lesions with embedded cavities:* Predominantly fibrotic lesions with embedded cavities do not as a rule yield to phrenic nerve surgery. In this group are included lesions that already show evidence of shrinkage as indicated by a partly deviated trachea and mediastinum, elevated line of demarcation between healthy and diseased lung, and peaking of the diaphragm (F. B., figure 2). One might at first be inclined to regard such lesions as suitable, since they are apparently in the process of contraction, and it is reasonable to suppose that, with the added relaxation of the lung and the elevation of the diaphragm which usually follow phrenic nerve paralysis, more contraction would take place and the cavities close. In only one case of this series, however, did this happen. In the others the disease either remained unchanged or the cavities actually increased in size. In the one case (E. B., figure 3) in which the diseased tissue continued to contract and the cavities finally closed, it required more than four years for closure to take place. In the meantime the patient was exposed to all the hazards of an open cavity.

(*3*) *Pneumonic consolidations:* Extensive consolidations do not as a rule respond to phrenic nerve interruption. Of 3 patients in this series with predominantly apical consolidations, with cavities 3.5 × 2.6,

FIG. 1



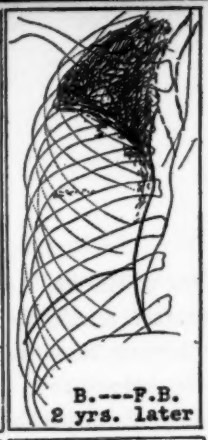
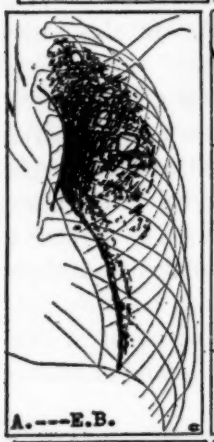
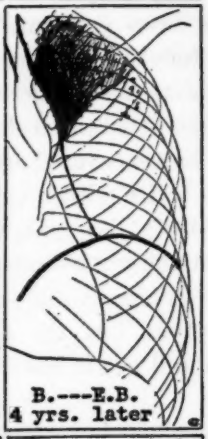
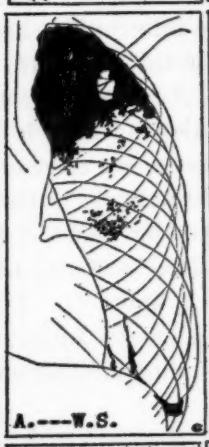


FIG. 2

FIG. 3







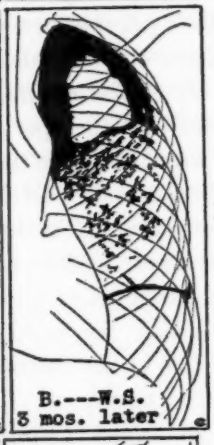
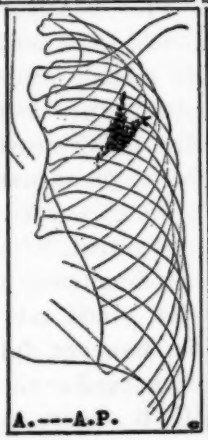
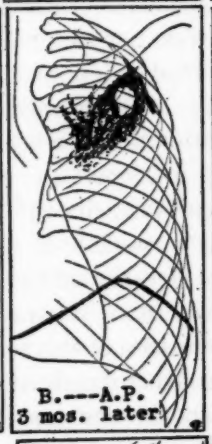
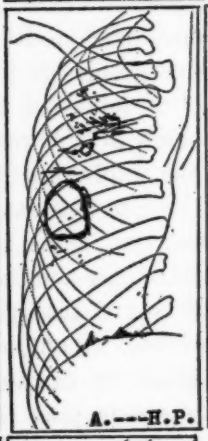


FIG. 4

FIG. 5.







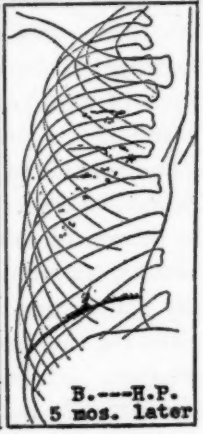
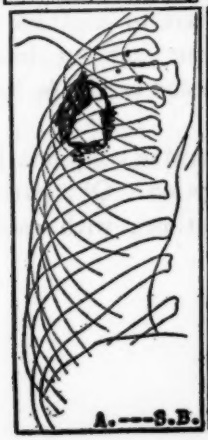


FIG. 6



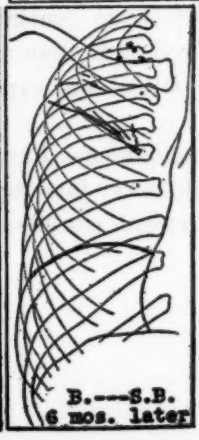


FIG. 7

FIGS. 1–7

2.3 × 2.2 and 2 × 2.5 cm. in diameter, respectively, not one was influenced favorably by paralysis of the diaphragm. In each instance the excavation of the consolidated part continued (W. S., figure 4). The same was true of another patient with consolidation and cavity formation in the middle third of the right lung.

(*4*) *Acute infiltrations:* There is general agreement that acute infiltrations do not as a rule respond to phrenic nerve interruption. This was true in the 2 cases in which it was tried in this series.

In the literature one also finds reference to large cavities in the axillary region as seldom responsive to phrenic nerve surgery. In the light of published reports it is reasonable to consider such lesions unsuitable.

Thus, there were, in this series, 30 patients with lesions which, in

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FIG. 1. Unsuitable lesion. A typical example of an apical cap cavity that is practically never influenced favorably by phrenic nerve interruption. In some instances improvement may follow the operation but it is largely in the surrounding infiltration and not in the cavity itself.

FIG. 2. Unsuitable lesion. A typical example of a densely fibrotic lesion with embedded cavities. Only rarely does this type of lesion respond to phrenic nerve interruption (see figure 3). The disease either remains unchanged or the cavities actually increase in size.

FIG. 3. Unsuitable lesion. An example of a densely fibrotic lesion with embedded cavities and deviation of trachea and mediastinum to the affected side, which responded to phrenic nerve interruption. Gradual contraction of the diseased area following operation resulted in complete closure of all cavities. However, it required about four years for closure to take place. In the meantime the patient was exposed to all the hazards of open tuberculosis. The possibility of an occasional brilliant result in unsuitable cases, however, should be kept in mind.

FIG. 4. Unsuitable lesion. Consolidation with excavation in left upper third. Extensive consolidations do not respond to phrenic nerve interruption. Invariably, excavation of the consolidated part continues.

FIG. 5. "Apparently suitable" lesion. Recent limited infiltration at level of left, second, anterior interspace which became worse and excavated in spite of a high, immobile diaphragm following phrenic nerve interruption. Lack of improvement was observed in more than half of patients with "apparently suitable" lesions, irrespective of the type or extent of disease present.

FIG. 6. "Apparently suitable" lesion. An example of a rapidly enlarging cavity in the middle third of the lung field which disappeared within five months after operation even though prior to operation the right diaphragm was almost immobile and the postoperative rise only slight, hardly enough to make a material increase in the collapse of the lung. Preoperative mobility of the diaphragm and the degree of postoperative rise are not necessarily determining factors.

FIG. 7. "Apparently suitable" lesion. A large cavity, 4 x 2.5 cm., just below the right clavicle which disappeared within three months after phrenic nerve interruption. In this patient the right pleura was so thick that it offered considerable resistance to the passage of the pneumothorax needle. Obviously a thick pleura is not necessarily a determining factor in the postoperative result.

retrospect, could be regarded as unsuitable. In only one case of the 30, or 3.3 per cent, was the disease improved and stabilized and all cavities closed. In 5 cases (16.7 per cent) there was improvement followed by relapse, and in 24 cases (80 per cent) the disease remained stationary or actually became worse after the operation.

It seems logical to conclude that the operation can be regarded as contraindicated in patients with lesions of the types noted, in the sense that no important benefit will follow. The contraindications, however, cannot be considered as absolute for occasionally a brilliant result does follow, or reduction in the size of the cavity, with associated clinical improvement, may be of distinct value in an individual case in preparation for some other form of surgical intervention. A careful review of the literature and personal experience, however, have convinced me that, when good results follow in these cases, they are the exception rather than the rule.

Results in "Apparently Suitable" Cases

Patients in this series with lesions not included under the heading unsuitable are regarded, in retrospect, as "apparently suitable" for phrenic nerve interruption, in the sense that good results followed in a significant percentage of the cases. Seventy-one of the 101 patients in this series thus fall in this category. The results are presented in table 2 and will be discussed under the following headings: (*1*) unimproved, (*2*) improved, (*3*) cleared.

Unimproved group: Even in this "apparently suitable" group lack of improvement was the most common observation. By this is meant that no material X-ray evidence of improvement in the tuberculous lesions was noted within three to six months after the phrenic nerve operation, or that an actual increase in the disease occurred. Fifty-two per cent of the "apparently suitable" patients in this series, 37 out of 71 patients, derived little or no benefit from the operation. The disease showed such slight improvement as to make no difference in the ultimate result (5 cases), remained stationary (14 cases), or continued to progress as before the operation (18 cases). Lack of improvement was observed in all kinds of cases with "apparently suitable" lesions, including both cases of early limited infiltrations without X-ray evidence of cavity and cases of advanced disease. The following summarized case is not unusual and illustrates this point well.

A. P., a white girl, 17 years of age, first came under my observation in July, 1934, for advanced tuberculosis with cavity formation involving the right upper lobe. Pneumothorax was established within a few days and the cavity quickly closed; the sputum became negative and the patient regained her health. In February, 1936, nineteen months after a successful pneumothorax had been established on the right, and at a time when the sputum was per-

TABLE 2

Results of phrenic nerve interruption in "suitable" cases

INVOLVEMENT	NUMBER OF CASES	CLEARED OR "CURED"	IMPROVED AND STABILIZED, ALL CAVITIES CLOSED	IMPROVED AND STABILIZED BUT SMALL CAVITY PERSISTS	MARKED IMPROVEMENT FOLLOWED BY RELAPSE	STATIONARY OR SLIGHT IMPROVEMENT	WORSE
Infiltration in upper third...	11	1	2		1	3	4
Infiltration in middle third..	5				1	4	
Infiltration in lower third...	3				1	1	1
Infiltration in upper and middle thirds.....	2					1	1
Infiltration throughout.....	11	1	2	2	1	2	3
Infiltration upper third with small cavity in upper (less than 3 cm. in diameter)...	18	2	2	5	3	5	1
Infiltration upper and middle thirds with small cavity in upper.....	5				3	1	1
Infiltration lower half with small cavities.....	1						1
Infiltration throughout with small cavities.....	6	2				2	2
Infiltration chiefly in middle third with large cavity (3 or more cm. in diameter)..	5	3					2
Infiltration upper third with large cavity below clavicle (3 or more cm. in diameter).....	4	1		1			2
Total.....	71	10(14%)	6(8%)	8(11%)	10(14%)	19(27%)	18(26%)

sistently negative and the patient apparently in good health, a small area of infiltration, represented by flocculent, grouped spots in the X-ray film, made its appearance in the outer half of the second anterior interspace in the left lung. The patient was put on bed-rest and a phrenic nerve evulsion performed on February 20, 1936, to give the left lung all the rest possible, short of pneumothorax. An excellent rise of the left diaphragm followed, but the infiltrative

area increased in extent, excavation began and positive sputum made its appearance (A. P., figure 5). Thus the phrenic nerve operation was a striking failure in a case of recent minimal tuberculosis. Pneumothorax was finally established on the left in June, 1936. The cavity closed within a few weeks and an excellent result followed.

Improved: Twenty-four, or 33.8 per cent, of the 71 "apparently suitable" patients derived benefit from the operation, in that the cavity was either closed or reduced in size or there was X-ray evidence of significant clearing of the associated disease, with lessening of toxaemia and improvement in clinical well-being.

However, in only 14 of these 24, or 58.3 per cent, did the improvement in the lung subjected to operation result in stabilization of the lesion so that no further therapy was required. In 6 of these, flocculent infiltration persists. In the other 8 patients the cavities, although greatly reduced in size, did not close completely and the threats of haemorrhage and spread of the disease remained.

In the remaining 10 patients of the 24 with improvement, or 41.7 per cent, the improvement, although marked at first, was in time followed by serious relapse, months and even years after the operation and in the presence of an elevated diaphragm which apparently was giving the lung the same degree of rest and relaxation that brought about the original improvement. This was a source of considerable disappointment, for not only did it mean in the end a waste of valuable time, but in some cases a lost opportunity for recovery as well. The following summarized observation illustrates this type of case.

W. R., a white male, 24 years of age, first came under my observation for advanced bilateral tuberculosis, with cavity formation and positive sputum, on October 8, 1934. He was put on bed-rest and pneumothorax was established on the right side on November 5, 1934, and a satisfactory collapse obtained. On January 12, 1935, a phrenic nerve crushing and scaleniotomy were performed on the left side. The left diaphragm rose a full interspace and the disease improved noticeably. The patient gained weight and strength, cough and expectoration became less, and apparently he was on his way to recovery. In due time the left diaphragm resumed partial function and descended to its former level. In October, 1935, ten months after the left phrenic nerve operation, the patient developed persistent cough and increased sputum and the cavity reappeared in the left upper lobe, below the clavicle. The cavity continued to enlarge in spite of bed-rest, and pneumothorax was established on February 28, 1936. The entire upper fourth of the lung, however, including

the site of the enlarging cavity, was adherent to the chest wall. Thoracoscopic study disclosed inoperable adhesions. The cavity could not be closed and the patient continued his down-hill course and died on September 28, 1936.

There is good reason to believe that, had a bilateral pneumothorax been established early, without the loss of time due to the phrenic nerve crushing, the result might have been different. Many adhesions can form and become formidable in ten months.

Cleared: In 10 patients, or 14 per cent, in this series of 71 "apparently suitable" cases, phrenic nerve interruption resulted in clearing of the disease in the lung subjected to operation, except for some fibrous strands and a few small, sharply defined, moderately dense spots. In 8 of these patients there were cavities of varying size in the lung for which the operation was performed, and in 2 there was infiltration without X-ray evidence of cavity. The result followed so shortly after operation and in such manner as to leave little doubt that the paralysis of the diaphragm was the responsible factor. Not only was the immediate result brilliant but the lungs have remained clear to this day (February, 1939), over an average period of more than six years after operation. The following case is typical.

H. P. first came under my observation in November, 1927, when he was 16 years of age. At that time he had far advanced tuberculosis with cavity formation involving both lungs. After one full year in bed, during which time he did not improve, therapeutic pneumothorax was established on the left side on November 10, 1928. A good result followed. Not only did the cavities in the left lung close, but the disease improved in the right lung as well and the patient in time was permitted regulated walking exercise. In November, 1930, following a mild head "cold," the disease in the right lung suddenly flared up and spread rapidly. The cavity in the middle third increased from 1 x 1.5 to 4 x 4 cm., the cough and expectoration became troublesome, and the patient began a down-hill course. On November 27, 1930, as an alternative treatment to bilateral pneumothorax, the right phrenic nerve was evulsed. Prior to operation the right diaphragm was almost immobile. After the operation the dome of the diaphragm rose only one cm., hardly enough to make a material increase in the collapse of the lung. Clinically, however, a most amazing result followed. The large cavity became progressively smaller with each week and within three months after the phrenic nerve operation not a trace of the cavity remained (H. P., figure 6). This lung has remained in excellent condition without evidence of active disease to the present time, more than eight years later.

Analysis of cases with cleared lesions: A critical analysis of the cases in which an excellent result followed phrenic nerve interruption leads to no concrete conclusions as to the type of case, among the "apparently suitable" patients, in which the operation can be undertaken with reasonable assurance of success. Good results were obtained in advanced disease and in unexpected situations. On the other hand, failures were encountered in minimal cases. In general, the location of the lesion was more important than its severity or extent, or the size of cavity, for good results were observed more frequently when the major lesion was situated below the clavicle, particularly in the middle third of the lung field, and when the cavity was isolated, thin-walled and surrounded by nearly normal lung tissue. There were, however, important exceptions.

In one case in which a favorable result occurred, a cavity, measuring 4 × 2.5 cm., situated below the middle of the clavicle at the level of the second rib anteriorly, was surrounded by a thick wall. Although thick-walled cavities as a rule do not yield to phrenic nerve surgery, this cavity disappeared completely within three months after operation (S. B., figure 7).

Another case (F. T.), with multiple cavities in the upper half of the lung, the largest of which measured 4.5 × 5.5 cm., is also striking. The patient was ill for five years, with sanatorium care for three. At the time the right phrenic nerve was evulsed, the disease was far advanced, involving both lungs, and the patient was losing ground on bed-rest. This was hardly a case to be selected for phrenic nerve surgery. Yet all cavities in the right lung disappeared within three to four months and the patient gained rapidly in weight from 113 to 131 pounds (F. T., figure 8).

FIGS. 8, 9, 10, 11, 12 & 13. Other "apparently suitable" lesions in this series that responded to phrenic nerve interruption. For descriptions see text. Good results, such as closure of cavities and clearing of disease, follow in less than 20 per cent of patients with "apparently suitable" lesions and can be obtained in advanced disease, in unexpected situations and in apparently unsatisfactory cases. In general, the location of the lesion is more important than its severity or extent or size of cavity. Good results are more frequent when the major lesion is situated below the clavicle, particularly in the middle third of the lung field, and when the cavity is isolated, thin-walled and surrounded by nearly normal lung tissue. The presence or absence of cavity, however, is not of determining importance in the final result.

FIG. 14. "Apparently suitable" lesion. Marked improvement followed by serious relapse after permanent phrenic nerve interruption. The initial improvement was striking and reached its peak by the end of the fifth month. After that the disease remained stationary for seven months, only to undergo serious relapse. Thoracoplasty should have been resorted to as soon as it became apparent that the phrenic nerve operation would not accomplish the desired result.

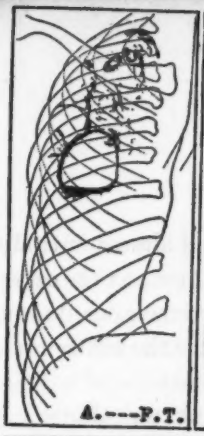
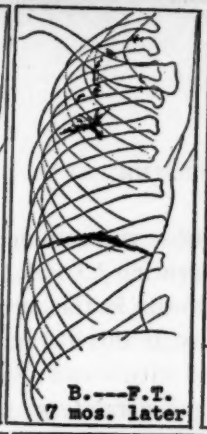


FIG. 8



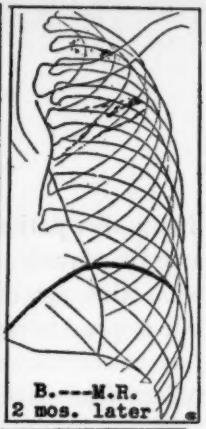
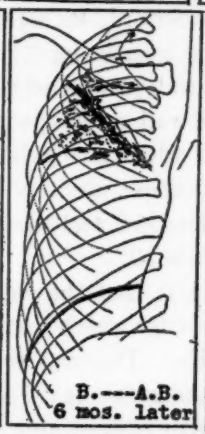
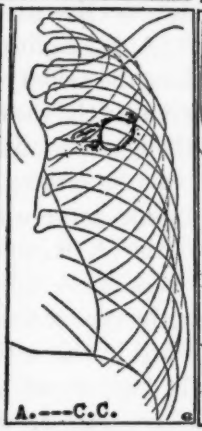


FIG. 9

FIG. 10





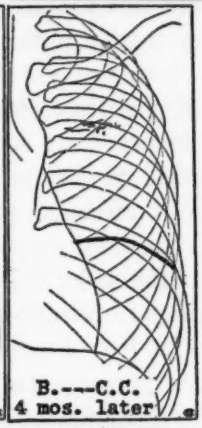


FIG. 11

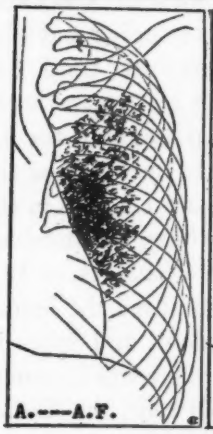
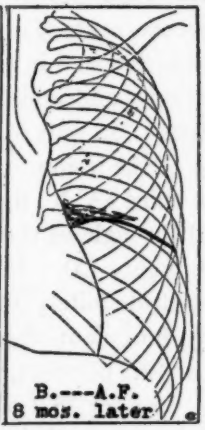
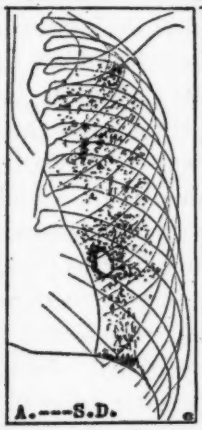


FIG. 12





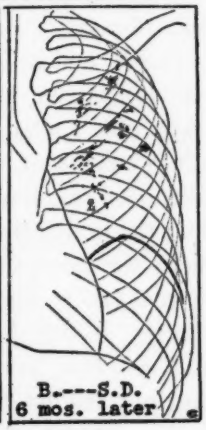
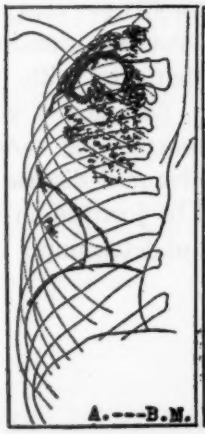
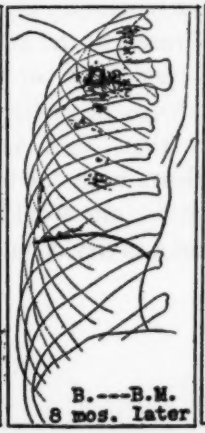


FIG. 13





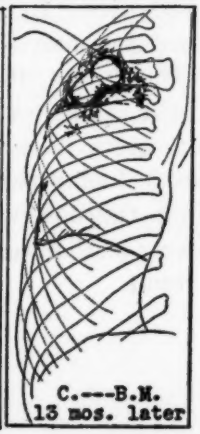


FIG. 14

FIGS. 8–14

In another patient (M. R.) the disease was confined almost entirely to above the clavicle, with a cavity measuring 2.3 × 1.2 cm., at the extreme apex. Although cavities of moderate size in the extreme apex do not as a rule respond to phrenic nerve surgery, in this instance the postoperative result was excellent; the cavity closed within two months, and a difficult problem (the patient was receiving contralateral pneumothorax) was solved in a simple and effective manner (M. R., figure 9).

In another patient (A. B.) cavities, measuring 2.5 × 2 and 2.5 × 2.5 cm., were situated along the axillary wall just below the clavicle, with the overlying tissue adherent to the chest wall, as was proved by an inefficient pneumothorax. Although laterally adherent cavities are said not to respond to phrenic nerve surgery, these cavities became noticeably smaller after the phrenic nerve operation and disappeared completely by the end of six months (A. B., figure 10).

At this point it is in order to indicate that the value of the operation in simple infiltrations, the type of lesion for which best results are claimed, was far from established in this series. This was true even in minimal cases. Among the 71 "apparently suitable" cases subjected to phrenic nerve interruption, there were 32 with infiltrations without X-ray evidence of cavity. In 11 the infiltration was centred in the upper and middle thirds, and in 5 in the middle third, and in 3 in the lower third. In 2 the infiltration was centred in the upper and middle thirds, and in 11 it was wide-spread throughout the lung. In only 2 patients of the 32, or in 6.2 per cent, was there clearing of the lesion. In one of these the infiltration was limited to the middle third (A. F., figure 12), and in the other the infiltration was wide-spread throughout the lung, but involved chiefly the lower three-fourths (S. D., figure 13). In 4 patients, or 12.5 per cent, there was improvement which definitely stabilized the lesion; however, infiltration, represented by flocculent shadows and spots in the X-ray film, has persisted. In 4, or 12.5 per cent, there was improvement but the disease later relapsed. In 9, or 28.2 per cent, the disease continued to advance. In the remaining 13, or 40.6 per cent, the disease either remained stationary (7 cases) or the improvement was insignificant (6 cases). Thus, only 18 per cent of patients with infiltrative lesions, without X-ray evidence of cavity, obtained a good result. This is not much better than that reported for series of unselected cases including patients with far advanced disease and large cavities. From this observation, one would be justified in concluding that the presence or absence of a cavity is not of determining importance in the final result.

The presence or absence of a free pleural space, the thickness of the pleura, the preoperative mobility of the diaphragm and the degree of postoperative rise or extent of tenting of the diaphragm were also not determining factors. In 3 patients in whom a favorable result followed, the pleura was so thick that it offered considerable resistance to the passage of the pneumothorax needle. In at least 3 patients with a good postoperative result there was little preoperative mobility of the diaphragm. In 2, with most striking and most unexpected result, the postoperative rise was slight, only one cm.

Summary of results in patients with "apparently suitable" lesions: Seventy-one of the 101 patients in this series (69.3 per cent) subjected to an independent phrenic nerve interruption could be considered, in retrospect, "apparently suitable" for the operation.

Only 34, or 47.9 per cent, of the patients with "apparently suitable" lesions benefited by the operation. The remaining 37 patients, or 52.1 per cent, with similar lesions and problems, derived no benefit from the operation.

Furthermore, in only 16 patients, or 22.5 per cent, was the result all that was desired, so that no further therapy was required. In this group, the lesions either cleared or there was marked improvement, with stabilization of the lesions and disappearance of all cavities.

In 8 patients, or 11.3 per cent, the improvement, although marked and lasting, did not result in complete closure of the cavities, and positive sputum persisted, necessitating some other form of collapse therapy for its elimination.

In 10 patients, or 14.1 per cent, the initial improvement following operation was in time followed by serious relapse.

These figures furnish a fair estimate of the value of phrenic nerve interruption as an independent collapse measure to close cavities and control tuberculous disease in its sphere of greatest usefulness.[2]

[2] Various postural and mechanical aids have been employed to enhance the effect of a paralyzed diaphragm, such as elevating the foot of the bed, applying pressure over the lower ribs with adhesive bandages, or lifting the diaphragm by specially constructed abdominal pads. While these procedures may be of help in isolated instances, they have been of little value in routine use. The same can be said for such supplementary operative procedures as scaleniotomy. Scaleniotomy was carried out in 57 patients in this series, in 52 at the same time with the phrenic nerve operation and in 5 some time later. The operation was of no value in these cases and, in retrospect, was not worth the extra effort or risk involved. More recently pneumoperitoneum has been used in conjunction with diaphragmatic paralysis and in some cases it has improved the result. The possibilities of this combination in individual cases should be kept in mind.

PHRENIC NERVE INTERRUPTION AS AN ALTERNATIVE TO ARTIFICIAL PNEUMOTHORAX OR THORACOPLASTY

There remains to be considered the relative value of phrenic nerve interruption, artificial pneumothorax and thoracoplasty as alternative, independent collapse therapy procedures.

As an alternative to artificial pneumothorax: Some authors, particularly O'Brien (9), advocate phrenic nerve interruption in place of artificial pneumothorax in cases characterized by early limited lesions and by small "moth-eaten" cavities, on the principle that phrenic nerve interruption is the simpler and more economical procedure and should be tried first. I have had opportunity to compare the relative merits of phrenic nerve interruption and pneumothorax therapy in the same individual in 39 patients in this series with bilateral disease, in whom the more diseased lung was treated with pneumothorax and the less involved side (many with early limited lesions) with a phrenic nerve operation as an alternative to bilateral pneumothorax.

Failure, in that the phrenic nerve interruption was either a useless undertaking (21 cases), or in that an initial improvement was in time followed by relapse (7 cases), was noted in 28 of the 39 patients, or in 71.8 per cent, and bilateral pneumothorax ultimately became essential. By this time, however, a selective collapse could be established in only 12. These 12 patients did well, although in 7 the tuberculosis in the lung subjected to the phrenic nerve operation had been advancing rapidly and undergoing extensive excavation, in spite of bed-rest and an immobile and elevated diaphragm.

In the remaining patients bilateral pneumothorax could not be established because of extensive pleural adhesions on the side on which the operation was performed, and the majority did not do well. It was felt that the time wasted on phrenic nerve interruption was largely responsible for the formation of extensive adhesions and was an important contributing factor to the ultimate poor result. As typical examples the reader is referred to the cases of W. R. and A. P., cited previously.

In only 11 patients of the 39 with a contralateral phrenic nerve operation (28.2 per cent) did the operation accomplish the desired result and eliminate the necessity of bilateral pneumothorax. In 4 of these the disease in the lung with the paralyzed diaphragm cleared, and in 7 the improvement resulted in stabilization of the lesions. Significant infiltrations, however, persist and future relapses seem likely to occur. In

contrast, the disease in the lungs collapsed by pneumothorax in these same 7 patients, although originally more advanced and more active, has shown greater healing in the same period of time and appears better stabilized and less likely to undergo relapse.

It naturally follows that phrenic nerve surgery should not be looked upon as a substitute for, and cannot take the place of, pneumothorax, but must be regarded as a supplementary form of therapy, important but secondary, to be used when the latter procedure cannot or should not be instituted.

As an alternative to thoracoplasty: The question of phrenic nerve interruption in preference to thoracoplasty presents a more difficult problem because of the seriousness of thoracoplasty, notwithstanding lowered operative mortality and greatly improved results following the modern operation. The following remarks are based on the observations made as a result of the study of the 106 patients in this series in whom phrenic nerve surgery was employed as an independent collapse measure with the hope of avoiding thoracoplasty.

Phrenic nerve interruption is certainly not justified in patients with cavities that experience has shown cannot be influenced by the operation (unsuitable cases), particularly if the patients are in good general condition for an immediate thoracoplasty. Not only will thoracoplasty be found essential later, but the time lost may prove disastrous. No one can predict what may happen to a given patient with an open cavity; haemoptysis, spontaneous pneumothorax or extension of the disease to other lung fields or other organs may occur in apparently quiescent cases and may result in death or permanent invalidism. This is borne out by the fact that of 31 patients in this series suitable for an immediate thoracoplasty, but subjected to phrenic nerve interruption in the hope of avoiding thoracoplasty, 3 died after sudden haemoptysis and 3 from progressive tuberculosis; 7 more became hopeless invalids. In retrospect, one sees that these tragedies might have been avoided had valuable time not been wasted on useless phrenic nerve interruptions and had thoracoplasty been performed when conditions were most favorable. Some investigators have also pointed out that, in poorly selected cases, phrenic nerve interruption may cause stagnation of secretions in the cavities and render the patient more liable to postoperative complications, or actually interfere with the success of the thoracoplasty in the collapse of the lower and middle lung fields (Lambert).

On the other hand, patients with "apparently suitable" lesions, that experience has shown will frequently improve following phrenic nerve interruption, have a great deal to gain from the operation. This is borne out by the experience with the 71 "apparently suitable" cases in this series. In 22 per cent, or approximately every fifth case, the cavities closed completely and the disease either cleared or became so stabilized that no further therapy was found necessary. These patients, of course, were spared the more serious and less desirable thoracoplasty. Experience with the other cases suggests that in an approximate additional 25 per cent the cavities will become reduced and the general condition improved sufficiently to increase the chances for closure of cavities and for recovery following thoracoplasty. Thus, practically every other patient with an "apparently suitable" lesion in whom thoracoplasty is considered has something to gain from a preliminary phrenic nerve interruption.

The risk in these cases is in delaying thoracoplasty after it has become apparent that progress following the phrenic nerve operation has reached a standstill, in the vain hope that somehow the cavities may yet close. Only rarely does this happen, and if thoracoplasty is not performed when the preliminary phrenic nerve operation has accomplished its maximum good the patient will not only lose valuable time but will be subjected to all the risks of open tuberculosis. The following case is typical:

B. M., female, 36 years of age, first came under my observation in July, 1937, at which time there was advanced tuberculosis involving the right lung, consisting of grouped and confluent flocculent spots in the upper half of the lung field, with a cavity, 3 x 3 cm. in diameter, at the level of the clavicle, and one, 1 x 1 cm. in diameter, just below the larger cavity. Pneumothorax was attempted but the upper half of the right lung could not be separated and the pneumothorax therapy was discontinued and a phrenicectomy carried out July 15, 1937. A satisfactory rise of the right diaphragm followed and it became immobile. The patient was kept on bed-rest and monthly fluoroscopic and X-ray examinations were made. The immediate improvement following the operation was striking. Within the first month the smaller cavity disappeared and the larger one was reduced to 3 x 1 cm. in diameter. The surrounding infiltration also showed evidence of clearing. Within five months after operation (December, 1937), the larger cavity was reduced to 1 x 1 cm. in diameter and practically two-thirds of the original infiltration had disappeared. This was the peak of the improvement. On March 19, 1938, eight months after the phrenic nerve operation was performed, and at a

time when progress was at a standstill, a right scaleniotomy was performed with the hope of completing closure of the cavity, but without success. The lung remained exactly in the same condition for the next four months. In July, 1938, virtually one year after the phrenic nerve operation, with the patient still on bed-rest, and the right diaphragm elevated and immobile, the cavity began to enlarge and within one month it again measured 3 x 3 cm. in diameter (B. M., figure 14). The remainder of the right lung did not show any increase in disease. A thoracoplasty was finally performed in order to close the cavity.

In retrospect, it is seen that the last seven months of treatment in this case represented a waste of time in the care of the patient. The cavity persisted and the patient was confined to bed. Although thoracoplasty was always kept in mind, it was delayed month after month in the vain hope that the phrenicectomy and bed-rest might still close the cavity or that the scaleniotomy might be successful. It was not until the cavity began to enlarge rapidly that a decision was forced. In one month all the ground gained following the phrenic nerve operation was lost and the patient was practically back where she had been a year before. The proper time for resort to thoracoplasty was five or six months after the phrenic nerve operation, as soon as it had become apparent that the cavity would not close. Had the thoracoplasty been performed at that time, the patient would seem clearly to have profited greatly from the preliminary phrenic nerve operation.

Fortunately, the good results of phrenic nerve paralysis become evident early within the first few months after operation, and this should make it possible to single out patients who are most likely to benefit from such planned delay of thoracoplasty in selected cases. The important thing is not to resort to a phrenic nerve operation when thoracoplasty is plainly indicated, and not to delay thoracoplasty beyond the time when the phrenic nerve operation has accomplished its maximum good.

PHRENIC NERVE INTERRUPTION AS AN ADJUNCT TO OTHER COLLAPSE MEASURES AND IN THE TREATMENT OF CERTAIN COMPLICATIONS OF PNEUMOTHORAX THERAPY

Phrenic nerve interruption was carried out in 16 patients in this series, either as an adjunct to other collapse measures or in the treatment of certain complications of pneumothorax therapy (table 1).

Ineffective pneumothorax: A number of writers report excellent immediate results, as high as 50 per cent, from a supplementary phrenic nerve operation, in the course of pneumothorax treatment, to close cavities held open by adhesions. There is little question that some cavities can and do close under such therapy, provided, of course, that the adhesions are of the relatively simple variety, such as strings, cords or bands, or the lung is suspended both from the apex and from the diaphragm. I believe from a study of the X-ray films published to supplement the texts, and from a description of the types of adhesions present, that in most instances the adhesions could have been severed by internal pneumonolysis, and that the latter is the more sensible, more direct and more scientific approach to the problem. It eliminates guess work.

If the adhesions are such as to render them truly inoperable, that is, if they are extensive, and if the cavity wall is directly adherent to the chest wall, there is general agreement that it is better to discontinue the pneumothorax and resort to bed-rest, with or without a phrenic nerve operation, depending upon the type of case. Sometimes unexpected closure of the cavity follows (10). In other cases thoracoplasty offers the better solution.

The only exceptions to the above rule are cavities near the hilum which fail to close under artificial pneumothorax. These cavities often close following phrenic nerve interruption and are an important indication for the operation. Their location near the hilum does not imply that they are central in the sense of being surrounded by healthy lung tissue. On the contrary, thoracoscopic study has convinced me that the walls of cavities near the hilum are often widely adherent to the vertebral gutter by inoperable adhesions.

Pneumothorax can be continued in some of these cases almost indefinitely without material benefit. Thoracoplasty is almost sure to result in failure, as the cavity is too deeply situated to be influenced. Paralysis of the diaphragm, especially when there is a good postoperative rise, and combined where possible with an upper lobe pneumothorax or oleothorax, will often close such cavities and solve simply and effectively what is apparently a hopeless problem. This application of phrenic nerve paralysis is an established procedure in many institutions and I have observed it in patients in my own experience, but not included in this series.

In the 2 cases of this series in which phrenic nerve interruption was used as an adjunct to artificial pneumothorax to relax apical adhesions

which prevented closure of cavities, it was partially successful in one and a complete failure in the other. In the latter case the adhesions were subsequently severed by internal pneumonolysis and the cavity promptly closed.

Judging from my experience, phrenic nerve interruption seems to be indicated in less than 3 to 5 per cent of patients with an ineffective pneumothorax.

Haemoptysis: I have used phrenic nerve interruption to control obstinate haemoptysis, when pneumothorax could not be instituted, in 2 cases in this series, but without success. Cases are well known, however, where the operation has been notably successful.

Troublesome cough: Phrenic nerve paralysis has been recommended to control harassing cough, and good results have been reported. Accumulated experience, however, has proved that the operation often fails and that in some cases it may have just the opposite effect and make the patient worse.

There were 5 patients in this series with cough sufficiently severe to warrant the operation. In only one of these did the operation appear to ease the cough; the other 4 patients received no relief whatever.

Two patients in this series, in whom phrenic nerve interruption was carried out to control their tuberculosis, experienced a marked change for the worse in their cough mechanism following the operation. They noticed difficulty in expectorating and developed a persistent hacking cough with frequent reflex vomiting. One case was right-sided and the other left. The loss of the expulsive power of the diaphragm was a distinct handicap to these two patients. Both individuals were thin and had poorly developed abdominal musculature. One of these patients received symptomatic relief from an abdominal support and the other from a thoracoplasty.

Discontinued pneumothorax therapy: Phrenic nerve interruption has been widely recommended as a precautionary measure against relapse after a successful pneumothorax had been discontinued, particularly if the discontinuance was forced by an early obliterating pleuritis. It is extremely difficult to appraise the value of the operation in such cases, as the operation is carried out at a time when the disease has responded to treatment. Phrenic nerve interruption was carried out in 2 patients in this series, for the above purpose, and in these 2 cases the lungs with the paralyzed diaphragm have remained free of disease six and seven years, respectively, after the operation, while at the same time the contralateral

lungs became the seat of progressive tuberculosis requiring artificial pneumothorax therapy.

Spontaneous pneumothorax: Phrenic nerve crushing was employed in one case in this series to abolish a spontaneous pneumothorax, on the theory that the resulting relaxation and selective collapse of the lung might produce closure of the tear in the lung parenchyma. In this particular instance it failed, although I have seen it succeed in another case of spontaneous pneumothorax, in a child following pneumonia. Aufses (5) mentions successful case reports by Goldschmidt and Weiss.

Empyema cavities: Phrenic nerve interruption was used in 3 patients in this series to help obliterate a pneumothorax space, the seat of a complicating empyema. In one case the empyema was predominantly staphylococcic, but could be controlled by repeated aspirations and closed tube drainage. The lower half of the lung was widely adherent to the diaphragm and chest wall, while the upper was collapsed by the pyopneumothorax, with the tuberculous disease apparently arrested. A permanent phrenic nerve interruption was performed, January 20, 1938, seventeen months after the empyema developed and apparently at a time of arrested progress. A good rise of the diaphragm followed and the remaining pneumothorax space was obliterated within one month after the operation. The empyema cavity has completely disappeared (February, 1939). Had the phrenic nerve interruption not succeeded, an extensive thoracoplasty would have been recommended.

Bronchopleural fistula complicating tuberculous empyema: Phrenic nerve interruption was performed in one patient in this series, who had a bronchopleural fistula complicating a tuberculous empyema. The operation was carried out at a time when the disease was becoming much worse. The operation appeared of decided value. Although there is evidence that the fistula reopens occasionally, the expectoration has almost disappeared and the patient is greatly relieved. The tuberculous empyema has also become stabilized and requires no aspiration.

Summary of results: The operation accomplished the desired result in about a third (37.5 per cent) of the 16 patients in this series subjected to phrenic nerve paralysis used not as an independent collapse measure.

COMPLICATIONS OF PHRENIC NERVE INTERRUPTION

An evaluation of phrenic nerve interruption is not complete without a discussion of the complications, both immediate and late, which may

follow the operation. Berry (11), 1930, in a review of 4,697 patients, found 1.2 per cent of operative complications, of which 4.5 per cent were fatal. Edwards and Stevens (3), 1938, in 1,000 consecutive phrenic nerve operations reported complications in 5.3 per cent and fatality in 1.6 percent. In the present series, significant complications, directly or indirectly attributable to the operation, were encountered in 6 (4.9 per cent), with death in 2 (1.6 per cent).

Cardiac failure was the outstanding complication and accounted for the 2 deaths. Apparently, phrenic nerve paralysis may bring about physiological changes of fatal embarrassment to the heart, particularly if the disease is advanced and bilateral and requires simultaneous collapse of the two lungs. Both cardiac deaths occurred in patients with advanced disease who were treated by the combined therapy of phrenic nerve interruption and contralateral pneumothorax. Edwards and Stevens report cardiac failure as a contributory cause of death in 9 patients after phrenic nerve paralysis.

In contrast to the experience cited above, 4 women patients in this series, with a permanently paralyzed diaphragm and a high postoperative rise, withstood the strain of pregnancy without difficulty. One of these women with a contralateral pneumothorax went through three successful pregnancies (C. C., figure 11). I have observed many patients living without any ill effects whatever from a high diaphragm, either on the left or right side.

The other important complications in this series were interference with the cough mechanism in 2 patients, and gastric disturbance in the form of belching and a sense of fulness in the stomach—annoying but not serious—in 3. The frequency of the latter complication following left sided phrenic nerve operations was 5 per cent (3 out of 60 patients).

There are, however, other possible ill effects associated with the operation which should be kept in mind, such as the risk to the patient from open tuberculosis while waiting for the good results of the phrenic nerve operation to become manifest, or the possibility that the operation may actually interfere in a physical sense with a future thoracoplasty. Reference has already been made to this phase of the problem.

The fact remains, however, that the treatment of tuberculosis does not always permit a safe and sure choice of therapy. Phrenic nerve interruption may, in individual cases, prove to be accompanied by the least risk.

TEMPORARY AS CONTRASTED WITH PERMANENT PHRENIC NERVE INTERRUPTION

Phrenic nerve interruption presents the necessity of a choice between a temporary paralysis and a permanent paralysis of the diaphragm. Unfortunately the choice is not always easy and not without disadvantages. This phase of the subject has been discussed frequently in the literature but without crystallization of opinion. Due to limitations of space only brief statements can be made.

Both temporary and permanent phrenic nerve interruption have their place in collapse therapy. A temporary phrenic nerve interruption is indicated when the problem is of an emergency nature, such as in haemorrhage or active disease requiring immediate collapse therapy, and when other collapse measures, such as pneumothorax or thoracoplasty, are in prospect. A permanent phrenic nerve operation, on the other hand, is indicated when the operation is carried out as the sole therapeutic measure in the attempt to cure the patient after other collapse procedures have been considered unsuitable, or are plainly contraindicated.

A temporary phrenic nerve interruption has the following disadvantages: It gives rest and relaxation for only a relatively short time (from three to six months, rarely as long as a year), and as a test procedure leaves much to be desired. If the phrenic nerve has been well crushed at the time of operation, it is not always easy to find the phrenic nerve again, and even if the nerve is located and recrushed the ensuing paralysis may not be satisfactory and becomes less satisfactory with each recrushing (O'Brien). Then, there is the possibility that little or no paralysis of the diaphragm may result or the paralysis of the diaphragm may become permanent. Of 65 patients with a temporary paralysis operation in this series, there was no diaphragmatic paralysis in one case (1.5 per cent), transient paralysis in 7 (10.7 per cent) and permanent paralysis in 8 (12.3 per cent).

A permanent phrenic nerve paralysis, on the other hand, has serious shortcomings of its own. Unless a good result follows, it may compromise the future welfare of the patient and seriously reduce his vital capacity. A permanently paralyzed diaphragm may render the patient liable to postoperative complications should thoracoplasty be necessary later, and may actually interfere with the success of the thoracoplasty in the collapse of the lower and middle lung fields (Lambert); or render the undertaking impossible or extremely hazardous because of cardiac

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embarrassment (Alexander). Most observers are agreed, however, that these difficulties are encountered almost entirely in patients with far advanced disease. I have encountered difficulty, following permanent paralysis, in only one patient in this series.

SUMMARY AND CONCLUSIONS

The immediate and late results following operation in a single series of 122 consecutive white adult tuberculous patients all of approximately the same social and economic status, performed during 1929 to 1938, are reviewed critically. The average period of postoperative observation was 25.9 months; more than 50 per cent of the patients were under observation from two to eight years. In 106 patients the operation was the sole measure employed to close cavities and control tuberculous disease, and in 16 it was used as an adjunct to other collapse measures and in the treatment of certain complications.

Criteria are given for evaluating the results, which are believed to make possible an improved, practical approach to the subject and to help resolve the present confusion and contradictory conclusions. Cases are classified, in retrospect, depending on the type of lesion present, as "apparently suitable" and unsuitable for phrenic nerve therapy, and the results in each group are appraised separately. The subject of phrenic nerve interruption is presented under four main headings, as follows: (*1*) the value of the operation as an independent collapse measure, with a brief analysis of phrenic nerve interruption as an alternative to artifical pneumothorax or thoracoplasty, (*2*) the value of the operation as an adjunct to other collapse measures, and in the treatment of certain complications of pneumothorax therapy, (*3*) complications of the operation, and (*4*) temporary as contrasted with permanent phrenic nerve interruption.

The experience gained from this series, considered in the light of a critical review of the literature, leads to the following conclusions:

1. The value of phrenic nerve interruption will in large measure depend on the type of case selected for the operation. Little or no good will follow the operation in a high percentage of unselected cases. In 3 to 5 per cent it may actually do harm.

2. As an independent collapse measure, the operation should not be undertaken in the presence of tuberculous lesions of the following character (unsuitable cases): apical cavities, 3 or more cm. in diameter; large

cavities with walls adherent in the axillary region; pneumonic consolidations; dense fibrotic lesions with embedded cavities and acute infiltrations. Only rarely does a good result follow. These unsuitable cases constitute approximately 30 per cent of the total of tuberculous patients.

3. Cases characterized by lesions other than those enumerated above may be considered "apparently suitable," in that good results will follow operation in a significant percentage of cases. This "apparently suitable" group makes up about 70 per cent of tuberculous cases.

4. If the results of the series of cases here reported may be taken as a criterium, no benefit will ensue from the operation, when used as the sole collapse procedure, in more than half of the cases considered "apparently suitable."

5. In approximately a quarter of the cases of "apparently suitable" type, improvement will follow as a result of the operation. However, in about 40 per cent of such cases in the series here considered, the initial improvement in the lung subjected to operation was followed in time by serious relapse, and in 60 per cent some other form of collapse therapy was found advisable in order to attain maximum stability of the lesion or closure of cavity.

6. In only 20 per cent of the cases with "apparently suitable" lesions subjected to operation did the disease in the lung with the paralyzed diaphragm clear or undergo such stabilization that no further therapy was required.

7. Although it appears that phrenic nerve interruption, as an independent collapse measure, can close cavities and arrest tuberculous disease in approximately 20 per cent of "apparently suitable" cases and can materially reduce the size of the cavity and improve the general condition in an additional 25 per cent, it must be admitted that there is no way of selecting these patients from among the "apparently suitable" type, except through trial and error. Should the operation be unsuccessful, not only is valuable time lost, but if the operation is chosen in preference to more certain collapse measures with a higher percentage of cure, such as pneumothorax or thoracoplasty, the time lost may prove disastrous.

8. For these reasons, phrenic nerve interruption should not be carried out as a choice therapy in patients in whom more certain collapse procedures can be instituted, except in special instances and under conditions of controlled follow-up. Moreover, when phrenic nerve interruption has

been used as a therapy of choice in selected cases, such collapse measures as pneumothorax or thoracoplasty should not be delayed beyond the point where the phrenic nerve interruption has accomplished its maximum good. Used within these limits the operation can accomplish great good in individual cases.

9. Phrenic nerve interruption also has value when used in conjunction with other forms of collapse therapy, and also for the following purposes, but only in selected cases: (*1*) closure of hilar cavities and control of disease in the lower half of the lung, combined where possible with an upper lobe pneumothorax or oleothorax, or upper stage thoracoplasty; (*2*) preparation for thoracoplasty (in a significant percentage of cases it may render thoracoplasty unnecessary); (*3*) relaxation of adhesions during ineffective pneumothorax therapy; (*4*) control of disease in the contralateral lung in the presence of bilateral disease requiring active collapse therapy of the two lungs; and, more rarely, (*5*) control of haemoptysis, (*6*) obliteration of an empyema cavity, (*7*) abolition of a spontaneous pneumothorax, (*8*) treatment of bronchopleural fistula, and (*9*) prevention of relapse after premature obliteration of pneumothorax space.

10. Both temporary and permanent phrenic nerve interruption have their place in collapse therapy. A temporary phrenic nerve interruption is indicated (*1*) when the problem is of an emergency nature, as in haemorrhage or active disease requiring immediate collapse therapy when other collapse measures cannot be instituted at the moment, and (*2*) when other collapse measures, such as pneumothorax or thoracoplasty, are in prospect. A permanent phrenic nerve operation, on the other hand, is indicated when the operation is carried out as the sole therapeutic measure in the attempt to cure the patient after other collapse procedures have been considered unsuitable, or are plainly contraindicated.

11. The danger to-day is not that too many phrenic nerve operations will be performed or that they will be undertaken in an indiscriminate and unthinking manner, but that the operation will be discarded. This would be unfortunate, for phrenic nerve interruption appears to have value in 15 to 25 per cent of tuberculous patients. At times it may be the simplest means for saving a patient's life. Obviously it should be taken into consideration when planning treatment. The operation, however, should be restricted to properly selected cases.

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REËSTABLISHMENT OF PNEUMOTHORAX[1,2]

ARTHUR REST

The subject of reëstablishment of a previously discontinued pneumothorax has received little attention from the phthisiologist in the past. While the literature of artificial pneumothorax is voluminous, this interesting phase of that all important method of therapy has been hardly considered. Voorsanger (1) as late as 1937 stated that "recompression of artificial pneumothorax has been seldom attempted, and in the majority of cases fails because of adhesions and obliterative pleuritis. It surprises us, therefore, that reinduction can be produced months and even years after reëxpansion."

So often the reappearance of a parenchymal lesion in a lung previously collapsed stimulates the need for some other form of therapy, usually thoracoplasty. Reëstablishing the pneumothorax is often taken for granted as an impossibility, unworthy of trial. Bosworth (2), in a personal communication, stated that when pneumothorax has once been tried and the lung permitted to reëxpand, he ordinarily, if more compression is needed, refers the case for thoracoplasty with the recommendation that pneumothorax be tried as a routine before this surgical procedure is instituted. The surgeon occasionally remarks when the thoracoplasty has been completed that the lung was so free from the chest wall that pneumothorax could probably have been easily reëstablished.

The length of time of maintaining an artificial pneumothorax has always been controversial and plays an important rôle in the reëstablishment of pneumothorax. Aycock and Keller (3) feel that the determining factor initiating reëxpansion is the condition of the treated lung and the general condition of the patient. The time element of collapse is of secondary importance. Twenty-one cases with exudative lesions were collapsed sixteen to twenty-five months with no reactivation, while fibrocavernous lesions were collapsed longer. They make the claim,

[1] From the Medical Department of the Sanatorium of the Jewish Consumptives' Relief Society, Spivak, Colorado.

[2] Presented at the regular meeting of the Denver Sanatorium Association, Denver, Colorado, October 25, 1938.

substantiated by Longo (4), that keeping the lung collapsed for a longer period of time is no guarantee against reactivation. Longo (4) firmly believes that pneumothorax should be discontinued after disappearance of the lesion and of symptoms. Zambianchi (5) contends that it is of some advantage to the patient not to continue pneumothorax much beyond the stage of clinical recovery and to terminate it voluntarily, with a fair chance that, should it become necessary in the future, recollapse may be possible. He feels that the possibility of reëstablishment depends on the duration of the pneumothorax. If the involvement is unilateral and of recent origin, the compression need not be continued as long as for a cavernous lesion of long duration. According to Burnand (6), a pneumothorax that results in the healing of a parenchymal lesion need not be continued indefinitely, if we were sure that it could be reestablished when necessary. Many phthisiologists consider this dictum with fear and hesitation, preferring to continue pneumothorax for years, giving small refills under high pressure and at long intervals until no further space is present.

The voluntary discontinuance of pneumothorax may be advantageous at a later date and stimulates one to theorize as to the potentialities of reëstablishment in these cases. The collapsed lung, through disease and disuse, loses a certain degree of elasticity and, with the resultant fibrosis and contraction, becomes reduced in volume. With reëxpansion the lung does not resume its previous size in the pleural cavity and probably leaves a space too small to be seen by X-ray. On the other hand, with ultimate compensatory emphysema and hypertrophy of the lung and with contraction of the hemithorax, this space is apparently obliterated; it is my belief, however, that the potential space still exists and that induction may again be possible in the sense that any initial pneumothorax may be established.

The literature is scant in the presentation of the subject of reinduction of pneumothorax. Shamaskin and Rogoff (7), in 1937, were able to reëstablish 9 cases out of 11. Their reinstituted cases had pneumothorax from four to twenty-four months and were discontinued from four to nineteen months. It is interesting to state that in their case of bilateral pneumothorax an effective collapse was secured a second time. The Fitzsimons General Hospital, in their report, (table 1, number X and table 2, number IX) also reëstablished a bilateral pneumothorax which had a collapse on the right side for five and one-half years and on the left for one and one-half years; they were reinstituted because of

TABLE 1

	NUMBER OF CASES DISCONTINUED AND REËSTABLISHED AT A LATER DATE	NUMBER OF CASES WHERE REËSTABLISHMENT WAS ATTEMPTED BUT FAILED	PERIOD OF TIME PNEUMOTHORAX WAS MAINTAINED BEFORE DISCONTINUED
I	8	2	(a) 11 months (e) 34 months (b) 1 month (f) 3 years (c) 2 months (g) 2 months (d) 5 months (h) 6 months
II	1	2	6 months
III	1	20	1.5 years
IV	2	5	(a) 3 years 4 months (b) 1 year 9 months
V	1	?	21 months
VI	3	About 20	(a) 14 months (b) 6 months (c) 2 months
VII	7	5	15 to 48 months
VIII	0	2	
IX	5	1	(a) 26 months (b) 5 months (c) 28 months (d) 1 month (e) 24 months
X	6	2	Average of 3 years
XI	6	3	(a) 1 year (b) 1 year (c) Right 5.5 years, left 1.5 years (d) 6 months (e) 2 years
XII	2	3	(a) 1.5 years (b) 2 years
XIII	2	0	(a) 6 months (b) 15 months
XIV	8	18	(a) 26 months (e) 4 months (b) 54 months (f) 5 days (c) 4 months (g) 2 months (d) 3.5 months (h) 12 days

TABLE 2

	NUMBER OF CASES DISCONTINUED AND REËSTABLISHED AT A LATER DATE	PRESENCE OR ABSENCE OF ADHESIONS IN THOSE REËSTABLISHED	REASONS FOR DISCONTINUATION OF PNEUMOTHORAX	REASONS FOR REËSTABLISHMENT OF PNEUMOTHORAX
I	8	(a) Several (b) Upper lobe adhesion (c) Several (d) Single (e) Several (f) None (g) Several (h) Single	(a) Obliterative pleuritis (b) By patient (c) Obliterative pleuritis (d) Reactions (e) Poor collapse (f) Adequate collapse (g) Poor collapse (h) Poor collapse	(a) Reactivation (b) Reactivation (c) Inadequate collapse (d) Reactivation (e) Reactivation (f) Reactivation (g) Inadequate collapse (h) Increase in symptoms
II	1	Upper lobe adhesion	Obliterative pleuritis	Reactivation
III	1	Present	Adequate collapse	Reactivation
IV	2	(a) Present (b) None	(a) Undetermined (b) Undetermined	(a) Reactivation (b) Reactivation
V	1	Apical	By patient	Reactivation
VI	3	(a) Upper lobe adhesion (b) Many (c) None	(a) Expand lung for thoracoplasty (b) By patient (c) By patient	(a) Inadequate collapse (b) Inadequate collapse (c) Inadequate collapse
VII	7	All had adhesions	Apparently adequate collapses	All had reactivation

VIII	5	(a) No adhesions (b) Adhesions (c) Adhesions (d) Adhesions (e) Adhesions	(a) Adequate collapse (b) Empyema (c) Adequate collapse (d) Poor collapse (e) Adequate collapse	(a) Reactivation (b) Replaced with air (c) Haemorrhage (d) Increase in symptoms (e) Positive sputum
IX	6	All had adhesions	(a) 4 Had adequate collapse (b) 1 By patient (c) 1 To collapse other side	(a) 4 Reactivation (b) 1 Inadequate collapse (c) 1 To replace acute effusion
X	6	(a) Upper lobe (b) None (c) Right (1), left (1) (d) Small (e) Adhesions	(a) Adequate collapse (b) By patient (c) Right adequate collapse, left by patient (d) By patient (e) By patient	(a) Reactivation (b) Inadequate collapse (c) Right reactivation, left inadequate collapse (d) Inadequate collapse (e) Inadequate collapse
XI	2	(a) Small apical (b) Apical and lateral	(a) Adequate collapse (b) Adequate collapse	(a) Reactivation (b) Reactivation
XII	2	(a) Undetermined (b) Undetermined	(a) By patient (b) By patient	(a) Inadequate collapse (b) Inadequate collapse
XIII	8	(a) Undetermined (b) Apical (c) None (d) Apical (e) Few (f) Undetermined (g) Undetermined (h) None	(a) Adequate collapse (b) By patient (c) Contralateral spread (d) Repeated accidental pneumothorax (e) Contralateral spread (f) Diagnostic pneumothorax (g) Adequate collapse (h) Pleural effusion	(a) Reactivation (b) Reactivation (c) Haemorrhage (d) Haemorrhage (e) Reactivation (f) Reactivation (g) Reactivation (h) Reactivation

reactivation and inadequate collapse, respectively. Shamaskin and Rogoff concluded that, because of reactivation of the lesion and return of symptoms, the basing of the duration of the pneumothorax on clinical recovery is not reliable and the collapse should be continued longer. Another deduction was that when adhesions follow the termination of the pneumothorax they appear almost immediately upon reëxpansion. If the lung does not become adherent immediately it continues to remain free. Hayes and Brown (8), in 1938, reported an alternating therapeutic pneumothorax, three times on the right and twice on the left, because of repeated reactivations. This case had pneumothorax for a period from seven to forty-five months with an interval of reëxpansion of one month to seven years. The first four pneumothoraces were terminated voluntarily and so probably facilitated the easily successful reinduction of the successive collapses. Rubin (9), in 1932, reëstablished a case four years after discontinuation because of inadequate collapse. This case had a pleural effusion. He stated that this complication, or even a history of obliterative pleuritis, should not deter one from attempting an induction or a reinduction. Michelis (10) reëstablished after several months three pneumothoraces complicated by pleural effusions. Morriss (11) reported a case of reëstablishment where pleural adhesions were present for more than one year. Kirch (12) successfully reinduced pneumothorax in 2 patients who had had a pleural effusion. In Zambianchi's (5) 8 cases of reëstablishment, 2 had a pleural effusion and 1 an adhesive pleuritis. Burnand (6), on the other hand, made the statement in 1934 that a pleural effusion, no matter how small and transitory, is responsible for pleural symphysis when the lung is allowed to reëxpand. He makes the statement that after discontinuance of pneumothorax the pleural space becomes obliterated. Amberson (13) and Douglas (14), in personal communications, stated that reëstablishment is impossible in those cases that have had an effusion for a prolonged period of time. Mantoux (15) reported a case that had pneumothorax for nine years which was discontinued voluntarily and reinduced six years later because of reactivation. Hutchinson (16) reported one case of pneumothorax which lasted five months and was reëstablished after an interval of six years and three months. Burrell (17) reinstituted pneumothorax in a patient seven months after the last refill and failed in 2 cases twenty months and twelve months, respectively, after cessation of pneumothorax. Pearson (18) reported a reëstablishment after a two-year interval. Zambianchi (5), in the seven-year period from 1924

to 1930, reinduced pneumothorax in 8 cases that had this therapy from three to eight months and were discontinued from three months to two years and nine months. Six of these cases had an effective collapse. Haensel (19), in 1928, described 2 cases in which phrenic exairesis allowed successful reinduction of the pneumothorax previously unobtainable because of pleural adhesions, and explained the favorable influence of this procedure on the relaxation of the base of the lung. Voorsanger (1), in 1937, after failing in an attempt to reinduce pneumothorax, was successful after a phrenic exairesis had been performed.

Of our 8 cases reported as being successfully reëstablished, 7 were instituted at the Sanatorium of the Jewish Consumptives' Relief Society and one at Bellevue Hospital, New York; the latter reëstablished case later became a patient at this institution.

CASE REPORTS

1: K. B., female, aged 33, was admitted for the first time in October, 1932. The onset was catarrhal in September, 1932. Examination revealed a recent cavity below the right clavicle. Sputum was positive. On October 14, 1932 a right pneumothorax was instituted and maintained under good negative readings. Adhesions formed rapidly. Manometric readings became positive and only small amounts of air could be introduced. In August, 1933, after eleven months of pneumothorax, no readings were obtained and pneumothorax was discontinued. The right infraclavicular cavity had disappeared. On August 25, 1933 a right phrenic exairesis was performed as a prophylactic measure. She left on April 18, 1934, lesion quiescent, sputum negative.

Patient was readmitted on March 28, 1938 because of reactivation. Sputum was positive. Examination revealed a small annular shadow near the right hilum and numerous infiltrations at the base (figure 1a). Subacute tuberculous laryngitis was a complication. On May 29, 1938, after an interval of four years and ten months, the right artificial pneumothorax was reëstablished easily (figure 1b) and refills from 300 to 500 cc. have been administered every seven to ten days with good negative readings. On October 12, 1938 a right intrapleural pneumonolysis was performed with a seemingly satisfactory result (figure 1c).

2: H. D., female, age 30, was admitted on September 11, 1937 for a left thoracoplasty. The onset of pulmonary tuberculosis was in March, 1929. A left pneumothorax was instituted in Europe in April, 1929 and was discontinued by patient in May, 1929 after a month, because of financial reasons. Examination revealed a lesion limited to the left upper lobe with cavitation (figure 2a). Sputum was positive. On October 19, 1937, after an interval of

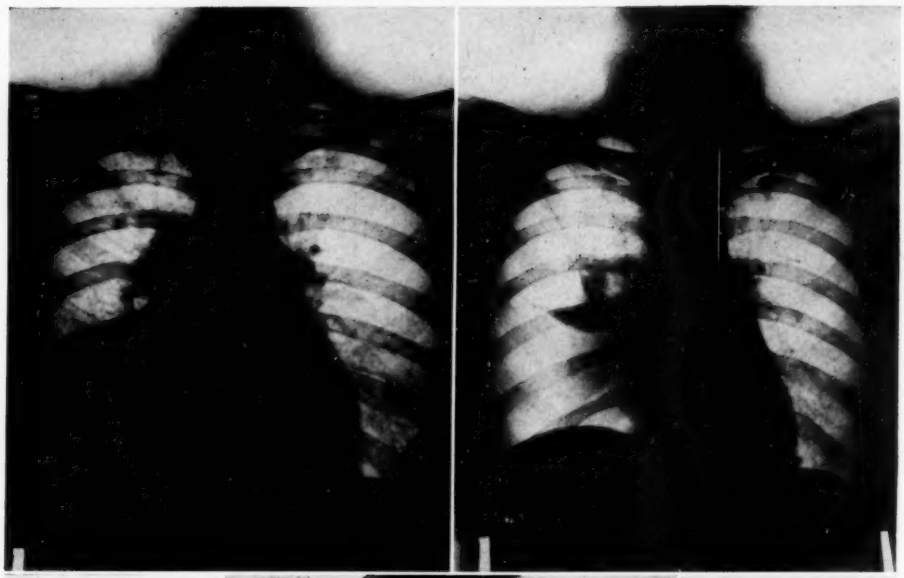

FIG. 1a

FIG. 1b

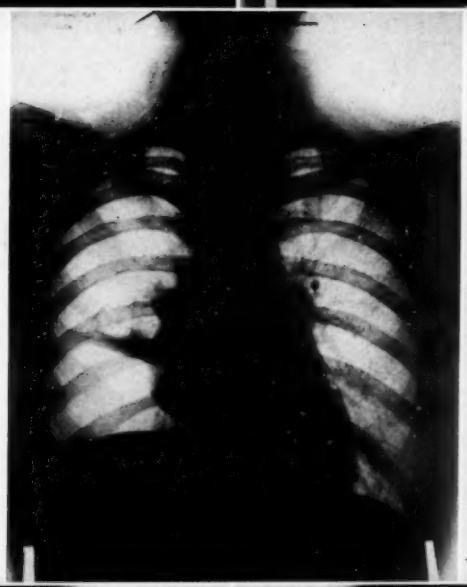

FIG. 1c

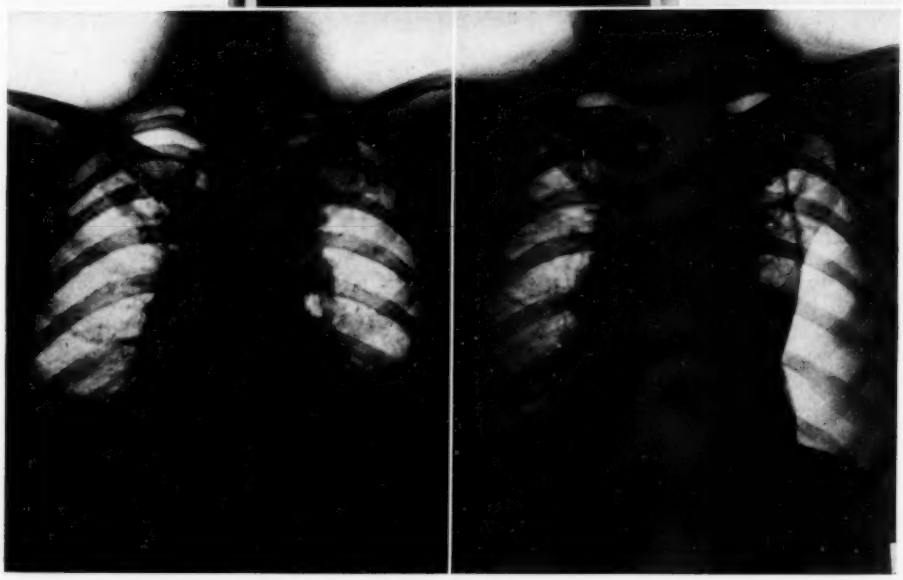

FIG. 2a

FIG. 2b

FIGS. 1a–2b

eight years and six months, the left pneumothorax was reëstablished (figure 2b) and has been continued with refills of 300 cc. every seven to twenty-one days with good negative readings. Pulmonary symptoms have disappeared. Sputum is occasionally positive. Collapse is partly contraselective and not entirely effective.

3: J. S., male, age 28, was admitted for the first time on January 21, 1935. Onset was catarrhal in December, 1934. There was a history of diabetes since October, 1932. Examination revealed extensive bilateral involvement with a cavity beneath the right clavicle. Sputum was positive. He left on September 24, 1935 with progression of the lesion in the right lung and a recent cavity in the left lung (figure 3a). Patient was readmitted on December 1, 1935. A left pneumothorax was instituted on March 13, 1936, and a right pneumothorax was established on April 25, 1936. On March 20, 1936 the left pneumothorax was discontinued because of poor collapse. The right pneumothorax was stopped on February 20, 1937 because of obliterative pleuritis. On August 30, 1937, after an interval of six months, the right pneumothorax was reestablished (figure 3b). Refills of 300 cc. were continued weekly with good negative readings until September, 1938, when it was discontinued because of ineffectiveness.

4: C. S., male, age 35, was admitted on July 20, 1936. The onset was catarrhal in 1935. A right pneumothorax was instituted on June 8, 1935 and refills from 500 to 900 cc. were given biweekly. In November, 1935, after five months of pneumothorax refills, this therapy was discontinued because patient did poorly. Examination revealed a right apical cavity (figure 4a) and sputum was positive. On August 20, 1936 the right phrenic nerve was crushed, but this procedure had little therapeutic value, and so, on May 28, 1937, after an interval of one year and seven months, the right pneumothorax was successfully reëstablished (figure 4b). Patient received refills of 300 cc. every seven days with good negative readings. The cavity has entirely disappeared. Sputum became negative.

5: E. F., female, age 35, was admitted for the first time on November 2, 1925. The onset was pleuritic in July, 1923. Examination revealed a bilateral lesion

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FIG. 1a. Before reëstablishment—a small annular shadow near the right hilum and numerous infiltrations at the base. Elevated right hemidiaphragm with paralysis.

FIG. 1b. Reëstablishment after four years, ten months—effective collapse prevented by numerous adhesions.

FIG. 1c. After internal pneumonolysis—adhesions severed with exception of a thick band—collapse is greater and procedure is seemingly successful.

FIG. 2a. Before reëstablishment—lesion limited to the left upper lobe with cavitation.

FIG. 2b. Reëstablishment after nine years, 6 months—collapse partly contraselective and not entirely effective.

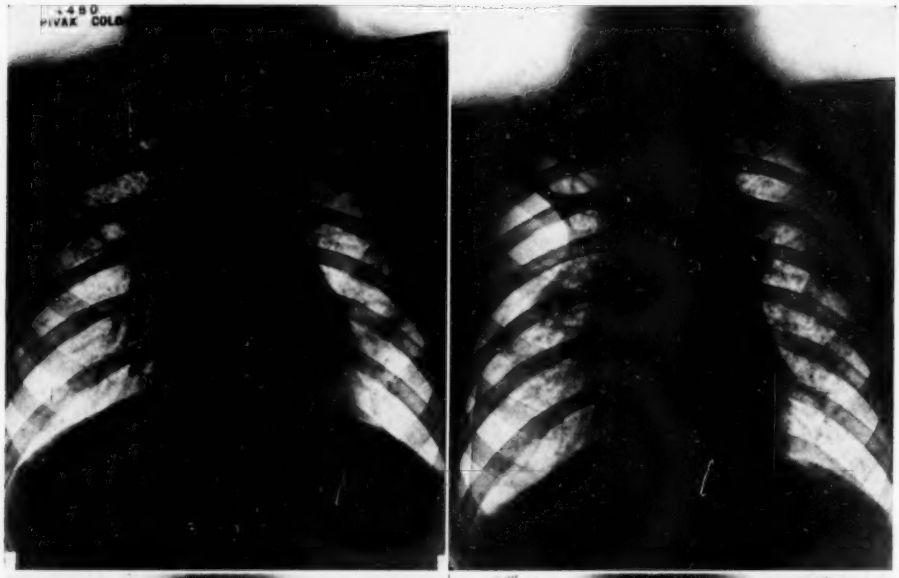

FIG. 3a

FIG. 3b

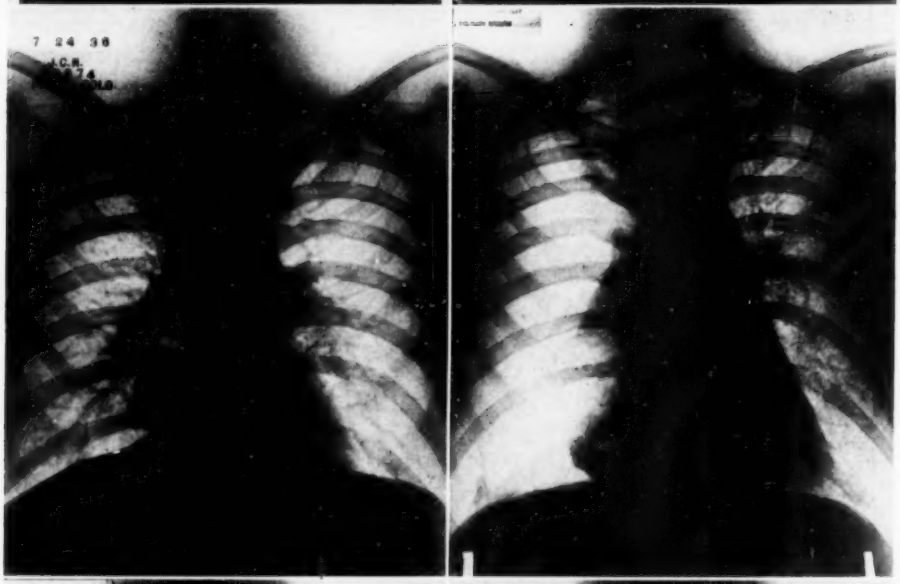

FIG. 4a

FIG. 4b

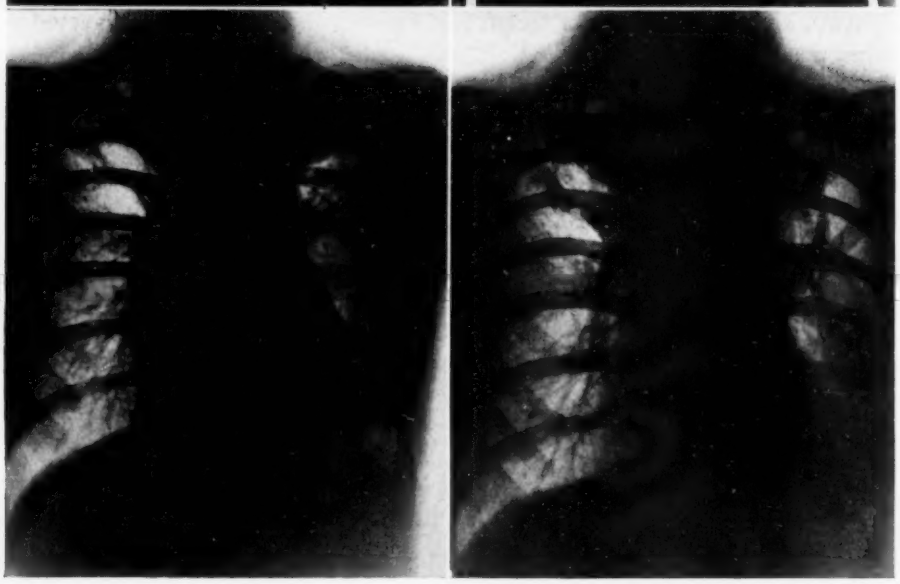

FIG. 5a

FIG. 5b

FIGS. 3a–5b

more extensive on the left. Sputum was positive. In October, 1926 a left pneumothorax was instituted and continued with good negative readings. She left in May, 1927, improved and sputum-negative and was readmitted on July 27, 1927 because of increased symptoms and positive sputum. Patient was now receiving from 200 to 700 cc. with good negative readings every seven to fourteen days. She had a small effusion in the left costophrenic angle. She left on April 1, 1928. In July, 1928, examination revealed a partial pneumothorax limited to the upper lobe and so it was discontinued because of poor collapse due to adhesions. Patient was admitted for the third time in January, 1936 because of reactivation and left on November 24, 1936. She entered for the fourth time on February 26, 1938 with marked symptoms of pulmonary tuberculosis and findings of cavities in the left upper lobe and an infiltrative lesion in the right lung (figure 5a). On May 13, 1938, after an interval of approximately ten years, a left artificial pneumothorax was reinstituted (figure 5b) and was continued every three to seven days with refills from 150 to 250 cc. with positive readings. On July 16, 1938 a left unsuccessful intrapleural pneumonolysis was performed, which was complicated by a pleural effusion, preventing further pneumothorax refills.

6: F. M., female, age 30, was admitted on February 16, 1937. Onset was with haemoptyses in June, 1929, and there were findings of a tuberculous bronchitis of the left upper lobe as diagnosed at Bellevue Hospital, New York (figure 6a). The left pneumothorax, instituted in May, 1930, was discontinued in March, 1933 because of adequate collapse. In June, 1936, because of reactivation and positive sputum, the pneumothorax was reëstablished at Bellevue Hospital, and she has been receiving refills from 100 to 250 cc. every two weeks with good negative readings. Patient has a good collapse (figure 6b) which has been complicated by several recurrent, moderately sized pleural effusions, disappearing promptly without leaving adhesions.

7: M. K., male, age 44, was admitted on July 21, 1936. Onset was catarrhal in 1934. Examination revealed a minimal right apical lesion with a scattered infiltrative lesion and cavitation in the left upper lobe (figure 7a). On August 3, 1936 a left pneumothorax was instituted, which appeared to be unsatis-

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FIG. 3a. Before reëstablishment—cavitation in both apices and near right hilum.

FIG. 3b. Reëstablishment after six months to collapse right hilar lesion—ineffective and discontinued.

FIG. 4a. Before reëstablishment—cavity in right clavicular region.

FIG. 4b. Reëstablishment after one year, seven months—cavity no longer visible—collapse entirely effective.

FIG. 5a. Before reëstablishment—cavitation in the left upper lobe and infiltrations in the right clavicular region.

FIG. 5b. Reëstablishment after ten years—sufficient collapse to perform a left intrapleural pneumonolysis, which was followed by a pleural effusion preventing further refills.

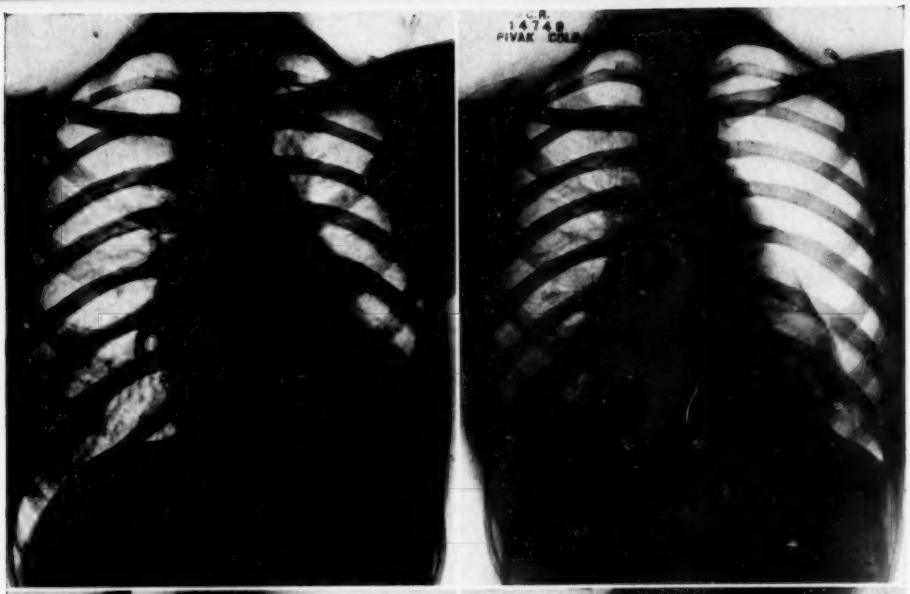

FIG. 6a

FIG. 6b

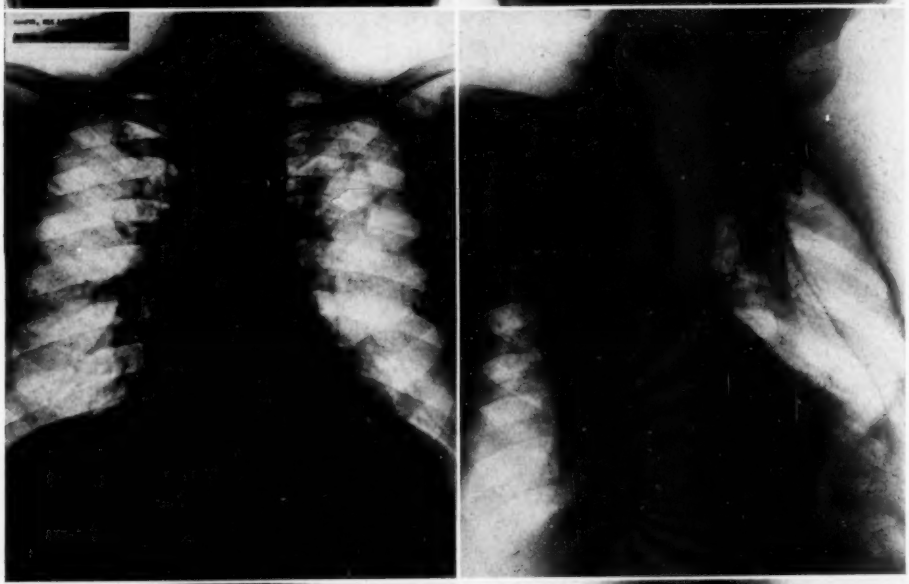

FIG. 7a

FIG. 7b

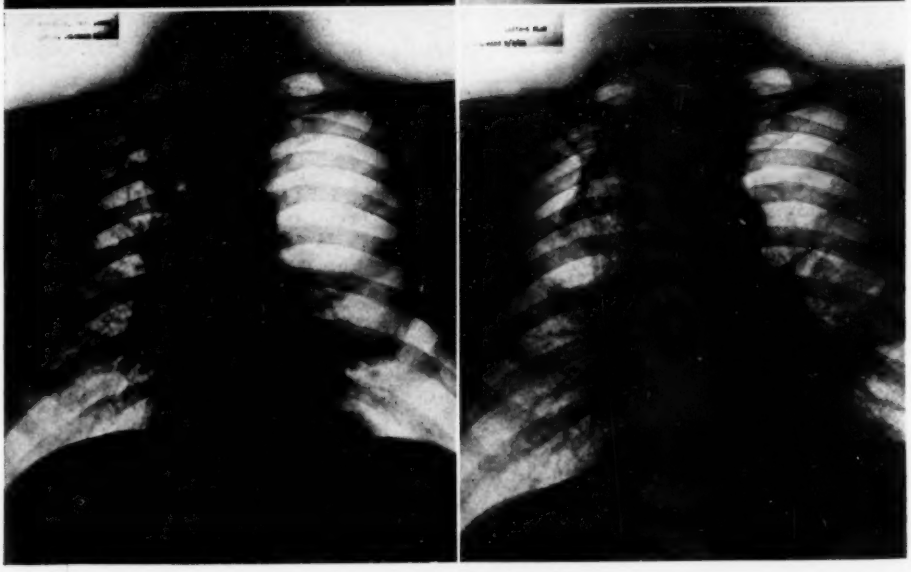

FIG. 8a

FIG. 8b

FIGS. 6a–8b

factory. Refills from 150 to 300 cc. were given every three to seven days with predominantly positive readings. Pneumothorax was discontinued on October 3, 1936. The left phrenic nerve was crushed on four occasions with a paralysis and rise only after the second attempt. The left pneumothorax was reëstablished on July 5, 1938, after an interval of twenty-one months (figure 7b). Refills from 100 to 300 cc. are given every three to seven days with predominantly positive readings. The cavity is difficult to delineate. Sputum is negative.

8: L. B., male, age 41, was admitted on March 1, 1938. The onset was catarrhal in 1931. Examination revealed suggestion of right infraclavicular cavitation and a left artificial pneumothorax (figure 8a), with the associated condition, diabetes mellitus. Persistent positive sputum led to collapse of the right lung on September 15, 1936, and was discontinued on February 8, 1938 because of ineffectiveness. The right pneumothorax was reëstablished on August 12, 1938, after an interval of seven months, and has been continued with refills of 250 cc. every seven days with good negative readings (figure 8b). The collapse is ineffective and may have to be supplemented by an intrapleural pneumonolysis.

The two cases in which reëstablishment failed were previously discontinued because of an obliterative pleuritis.

Since the literature only contains the individual experience of a limited number of authorities on this subject, I incorporated the aid of some of the leading tuberculosis institutions of the country in this study. Out of 70 sanatoria, 54 answered our questionnaire and only 13 had statistical data available from which tables 1 and 2 were prepared. From these tables it can be seen that the number of cases reported reëstablished were few, the largest being 8 from this Sanatorium (table 1, number I and table 2, number I) and the same number from the Glen Lake Sanatorium,

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FIG. 6a. Before reëstablishment—tuberculous bronchitis of the left upper lobe, diagnosed at Bellevue Hospital.

FIG. 6b. Reëstablishment at Bellevue Hospital after three years and continued at this institution. Collapse complicated by several moderately sized effusions, disappearing promptly without adhesion formation.

FIG. 7a. Before reëstablishment—cavitation of left upper lobe with a minimal lesion of the right apex.

FIG. 7b. Reëstablishment after twenty-one months—pneumothorax can only be seen on the oblique view and is effective.

FIG. 8a. Before reëstablishment—probable right infraclavicular cavity, a left artificial pneumothorax.

FIG. 8b. Reëstablishment after seven months—collapse shows a cavity in the right infraclavicular region and short adhesions preventing effective pneumothorax.

Oak Terrace, Minnesota (table 1, number XIV and table 2 number XIII). Even the attempts toward reinstitution were infrequent, as indicated by table 1.

SUMMARY OF TABLES 1 AND 2

Of the 135 cases included in tables 1 and 2, 52, or 39 per cent, were successfully reëstablished after being discontinued at one time; 83, or 61 per cent, failed in being reëstablished.

Of the 52 successful cases:

(A) 40, or 77 per cent, had adhesions
(B) 7, or 13 per cent, had no adhesions
(C) 5, or 10 per cent, were undetermined

Period of time pneumothorax was maintained before discontinued:

(A) 21, or 40 per cent, were maintained for less than one year
(B) 7, or 13 per cent, were maintained from one to two years
(C) 7, or 13 per cent, were maintained from one to three years
(D) 8, or 15 per cent, were maintained from one to four years
(E) 7, or 13 per cent, were maintained from three to four years
(F) 1, or 2 per cent, was maintained from four to five years
(G) 1, or 2 per cent, was maintained from five to six years

Reasons for discontinuing pneumothorax in these 52 cases:

(A) 3, or 6 per cent, had an obliterative pleuritis
(B) 4, or 8 per cent, had a poor collapse
(C) 12, or 23 per cent, were discontinued by patient
(D) 22, or 40 per cent, had adequate collapse
(E) 1, or 2 per cent, was discontinued because of reactions
(F) 1, or 2 per cent, had empyema
(G) 1, or 2 per cent, was discontinued to collapse the other lung
(H) 2, or 4 per cent, had a contralateral spread
(I) 1, or 2 per cent, had repeated accidental pneumothoraces
(J) 1, or 2 per cent, had pleural effusion
(K) 1, or 2 per cent, was distontinued after diagnostic pneumothorax
(L) 1, or 2 per cent, was permitted to reëxpand for thoracoplasty
(M) 2, or 4 per cent, were discontinued for undetermined reasons

Reasons for reëstablishment of pneumothorax in these cases:

(A) 32, or 62 per cent, had reactivation
(B) 12, or 23 per cent, had an inadequate collapse
(C) 2, or 4 per cent, had increase in symptoms
(D) 2, or 4 per cent, were reinduced to replace an effusion
(E) 1, or 2 per cent, had positive sputum
(F) 3, or 6 per cent, had haemoptyses

CONCLUSIONS

1. Reëstablishment of pneumothorax is possible more often than was formerly believed and should always be tried where further compression is desired.

2. Voluntary reëxpansion of the lung offers the greater chance for reinduction and the second pneumothorax might even be more effective than the original collapse.

3. Repeated effusions do not necessarily result in symphysis and a history of this complication or of an obliterative pleuritis does not preclude the absence of a free pleural space and should not prevent the attempt of reëstablishment.

4. A case was presented where reinduction was successful after a phrenic exairesis in a patient whose pneumothorax was previously discontinued because of apparent absence of a free pleural space. It is difficult to state whether reëstablishment was merely a coincidence or was made possible by the phrenic exairesis.

5. The advent of intrapleural pneumonolysis might aid effective reinduction by producing a satisfactory collapse in cases previously ineffective, because of adhesions, and hence, discontinued.

6. The long duration of a pneumothorax and the interval after a pneumothorax was abandoned are no contraindications of reëstablishment.

7. The voluntary abandonment of pneumothorax by the physician or the patient without consent, although apparently conducive to the greater percentage of reëstablishments, included the larger number that required further compression at a later date because of reactivation and inadequate collapse.

8. Finally, reëstablishment of pneumothorax, although possible, is far from a general attainment. Consequently, in such a disease as pulmonary tuberculosis, characterized frequently by relapse, it seems plausible to continue pneumothorax indefinitely and to consider its abandonment with reluctance.

I wish to express my deep appreciation and acknowledgement to the staffs of the following institutions who supplemented with their clinical data that of the Sanatorium of the Jewish Consumptives' Relief Society: Fitzsimons General Hospital, Denver, Colorado; National Jewish Hospital, Denver, Colorado; Swedish National Hospital, Denver, Colorado; Metropolitan Life Insurance Company Sanatorium, Mt. McGregor, New York; Lenox Hill Hospital, New York; Davidson County Tuberculosis Sanatorium, Nashville, Tennessee; North Reading State Sanatorium, North Wilmington, Massachusetts; Hamilton County

Sanatorium, Cincinnati, Ohio; Nopeming Sanatorium, Nopeming, Minnesota; Rhode Island State Sanatorium, Wallum Lake, Rhode Island; Wisconsin State Sanatorium, Statesan, Wisconsin; Glen Lake Sanatorium, Oak Terrace, Minnesota; Pottenger Sanatorium, Monrovia, California.

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FATALITY RATES IN PULMONARY TUBERCULOSIS[1]

Their Trend Based on Roentgenological Studies of 8,000 Patients

HOMER L. SAMPSON

In respect to the diagnosis and treatment of pulmonary tuberculosis to-day, two pertinent questions may be asked. (*1*) Is the pulmonary tuberculosis of to-day being diagnosed earlier than it would have been a quarter of a century ago? (*2*) Has a patient with pulmonary tuberculosis to-day a better chance of recovery than was the case twenty-five years ago? Both of these questions were put to a number of eminent physicians, qualified to give an opinion, and the answer was almost invariably "yes" to both. However, a few qualified their replies in one way or another.

If we were to accept some of the statistics recently published, it would seem that the patient with pulmonary tuberculosis discovered to-day has no better chance of recovery than a similar patient of a quarter of a century ago. It is hard to believe that such figures reveal the true aspect of conditions. For many years we have been interested in this problem, and we have developed a somewhat novel scheme for studying it and detecting any changes in fatality rates in the three classification groups of pulmonary tuberculosis, namely, minimal, moderately advanced and far advanced. A "wooden book" was constructed, in which it is possible to tabulate individually three or four thousand cases. Cases are arranged in periods of time and according to the extent of pulmonary tuberculosis present (minimal, moderately advanced, etc.), and also according to the predominant type of lesion (exudative, productive, etc.). Spaces are reserved for such cardinal factors as the presence or absence of tubercle bacilli, the physical signs, certain symptoms, the method of treatment, the amount of walking exercise the patient was able to handle at the time of discharge, the behavior of the disease subsequent to discharge, the treatment after leaving the sanatorium and the condition of the patient at the present time. Information regarding the patient after his discharge was obtained from the yearly reports which the patients returned. All of this evidence, both during

[1] From the Trudeau Sanatorium, Trudeau, New York.

residence and after discharge, was tabulated with colored thumb tacks, which revealed very vividly the happenings as they took place. Realizing that there are obvious weaknesses in studies of this nature, it nevertheless can be said that we are in better control of the problem than if we handled the cases in larger and more heterogeneous groups.

Granting that to-day many patients pursue the long-established hygienic-dietetic treatment route to recovery, almost as many, or considerably more in some places, avail themselves, at the discretion of the physician, of the different forms of collapse therapy. It cannot be said to-day that collapse therapy is used only after rest has seemingly failed. Many patients receive some form of collapse therapy almost immediately following the diagnosis.

Another important phase of the work was that all of these groups could be studied on the basis of a given period of time after discharge. This time interval was placed at six years. The reason for selecting six years was that other studies of postdischarge condition of patients revealed that the death curves for various groups and classifications of patients come close together about this time. Put another way, the life expectancy for far advanced cases was closer to that of the moderately advanced at this point than it was in the earlier years; also, the moderately advanced was closer to the minimal at this sixth milestone than it was in the first year after discharge. (See chart 1.)

Before we could study these groups comparatively, it was necessary to be reasonably sure that the groups were comparable. To determine this, 1,000 cases of eight different periods of time were selected. The patients of these groups were resident at Trudeau Sanatorium during the following periods:

1st group: April, 1905 to July, 1911
2nd group: July, 1911 to February, 1916
3rd group: February, 1916 to February, 1920
4th group: February, 1920 to February, 1924
5th group: February, 1924 to August, 1927
6th group: August, 1927 to January, 1931
7th group: January, 1931 to June, 1935
8th group: the current 1,000 cases

Each of these groups was subdivided into the respective classifications, according to the National Tuberculosis Association standards, namely, nontuberculous, suspect, minimal, moderately advanced and far advanced disease. The standards by which these classifications were made

did not vary much during these periods of time, also the same physicians applied these standards. Hence the groups are more constant because of less variation in individual opinion. (See chart 2.)

For comparison, too, it becomes necessary to consider how these cases came to light. What brought about the diagnosis? In the first two groups, and probably in the third, it is safe to say that almost all of these patients came to the doctor complaining of illness, and that because of this the diagnosis was made largely by history, symptoms, physical signs and sputum examinations. In the last five groups the roentgeno-

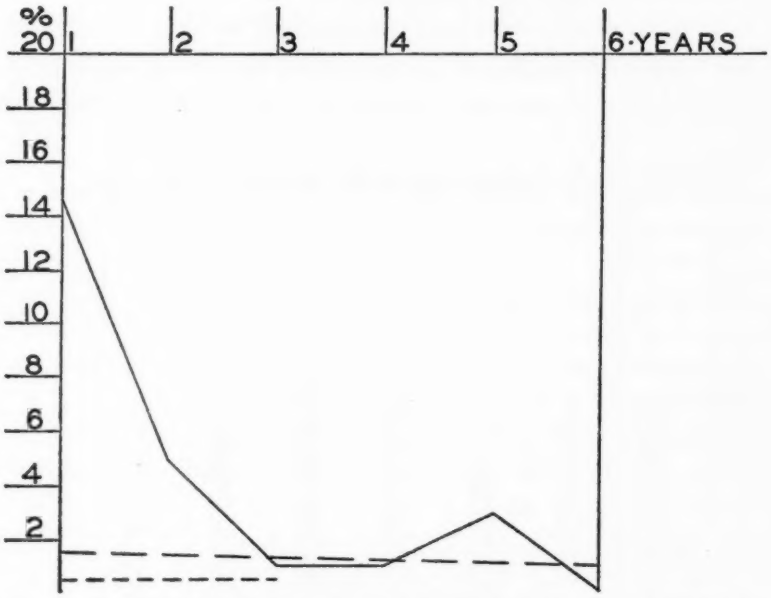

CHART 1. Yearly death rate up to six years, for minimal (------), moderately advanced (— — —), and far advanced (——) pulmonary tuberculosis. Sixth thousand (1927–1931) group.

gram undoubtedly played a very important part in the discovery and diagnosis of a great majority of the cases. It is also safe to say that many of the cases in these latter periods would have remained undiagnosed for some time had it not been for the roentgenogram, since in many of the cases physical signs were absent and bacilli were not demonstrated in the sputum. Hence, the first question at the beginning of this paper can be answered by "yes." Obviously a careful analysis of each thousand cases should bring to light trends, if such were the fact.

A statistical study of the first thousand cases (1905–1911) revealed that the diagnoses were made in the following ratios:

Nontuberculous 3 (.3 per cent)
Suspect 4 (.4 per cent)
Minimal (incipient in those days) 360 (36 per cent)
Moderately advanced 615 (61.5 per cent)
Far advanced 19 (1.9 per cent)

Dead from Pulmonary Tuberculosis at the End of Six Years
Minimal 19 (5 per cent)
Moderately advanced 163 (26 per cent)
Far advanced 9 (47 per cent)
Total death rate for all classifications 19 per cent

A few important statistical features stand out in the above analysis. (*1*) It is to be noted that there was an extremely low incidence of non-

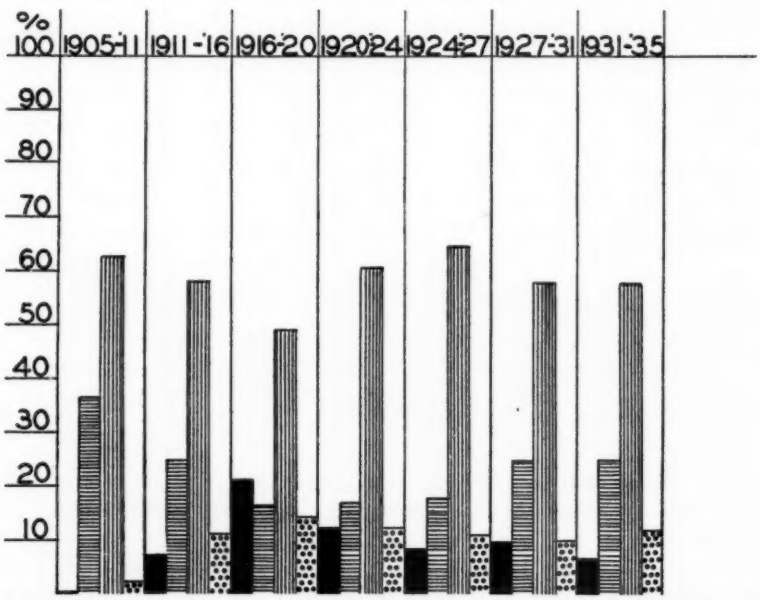

CHART 2. Showing the seven 1,000-cases grouped according to their respective periods of time and also showing the ratios of different classifications in the respective groups. Nontuberculous and suspect (■) Minimal (▤) Moderately advanced (▥) Far advanced (▪)

tuberculous, suspect and far advanced cases. It is also to be remembered that the roentgenogram was rarely used in this group to make the diagnosis. As the result of a study of the second group, it seems reasonable

to assume that in the first group of 1,000 cases many of the nontuberculous and suspect cases had been diagnosed as minimal or moderately advanced. If this were the case, and they (the nontuberculous and the suspect) were eliminated, the tuberculosis death rate in both the minimal and moderately advanced groups would naturally go up appreciably. (*2*) Assuming that there may have been 15 to 20 per cent nontuberculous and suspect cases in this first group, as there were in the second and third groups, then the tuberculosis death rate for the whole group of 1,000 cases, which was 19 per cent, would also be raised appreciably. It might be assumed that the death rate in those cases that had definite tuberculosis would be 23 or 24 per cent. It cannot be overlooked that irregularities in the diagnoses play havoc with percentages and calculated death rates.

The second thousand cases proved a more interesting study because it was during this period (1911–1916) that about 50 per cent of the patients were examined roentgenologically after having been admitted to the sanatorium. However, most of the thousand cases came to the institution on the same basis as did the first group. Also, in this group the roentgenogram did not play a part in the original classification of the cases. Years later these same cases (the 500 who had had roentgenograms) were reclassified upon the basis of what the roentgenogram revealed. Hence, it was possible from a study of this second group, both before and after reclassification, to draw some conclusions regarding the correct classification of the first group. The following is an analysis of the second group:

Diagnosis before Reclassification

Nontuberculous 11 (1.1 per cent)
Suspect 38 (3.8 per cent)
Minimal 331 (33.1 per cent)
Moderately advanced 594 (59.4 per cent)
Far advanced 26 (2.6 per cent)

(Again, it is to be noted that there is an unusually low rate in both the nontuberculous and far advanced cases.)

Diagnosis after Reclassification

Nontuberculous 114 (11.4 per cent)
Suspect 45 (4.5 per cent)
Minimal 244 (24.4 per cent)
Moderately advanced 532 (53.2 per cent)
Far advanced 65 (6.5 per cent)

The death rate at six years was 20 per cent, almost the same as for the first group. This is reasonable proof of the similarity of the groups. However, the analysis also reveals, as was inferred in the first group, that if only the definite cases of tuberculosis were considered (excluding the nontuberculous and suspect) the death rate would be 23.5 per cent.

The third thousand cases, resident during the years 1916–1920, present interesting points for discussion. (*1*) Most of these patients, as in the preceding groups, sought the physician because of symptoms of illness. However, a certain unknown percentage were "accidentally" discovered through roentgen-ray examination. (*2*) All of these cases were originally diagnosed and classified upon the basis of the clinical evidence, physical signs and laboratory findings. The roentgenogram played little part in the classification in those days. Later, however, all these cases which had had routine admission roentgen-ray examinations at the sanatorium were reclassified in consideration of what the roentgenogram revealed.

Upon the Original Classification

Nontuberculous 62 (6.2 per cent)
Suspect 84 (8.4 per cent)
Minimal 194 (19.4 per cent)
Moderately advanced 588 (58.8 per cent)
Far advanced 72 (7.2 per cent)

Reclassification changed these percentages appreciably, so much so that death rates calculated upon only those who had tuberculosis would be materially affected.

Reclassification

Nontuberculous 161 (16.1 per cent)
Suspect 43 (4.3 per cent)
Minimal 169 (16.9 per cent)
Moderately advanced 487 (48.7 per cent)
Far advanced 140 (14 per cent)

The death rate was naturally figured upon the reclassification, and revealed the following: dead of tuberculosis at the end of six years (excluding the nontuberculous and suspect cases) 25 per cent. (Interestingly, this was the highest death rate at six years for all of the seven 1,000-groups.)

A survey of these first three 1,000-groups now reveals that the accumulated death rate at six years was about the same for each group. However, the rate for the different classifications (minimal, etc.) varied appreciably. (See charts 3, 4, 5 and 6.)

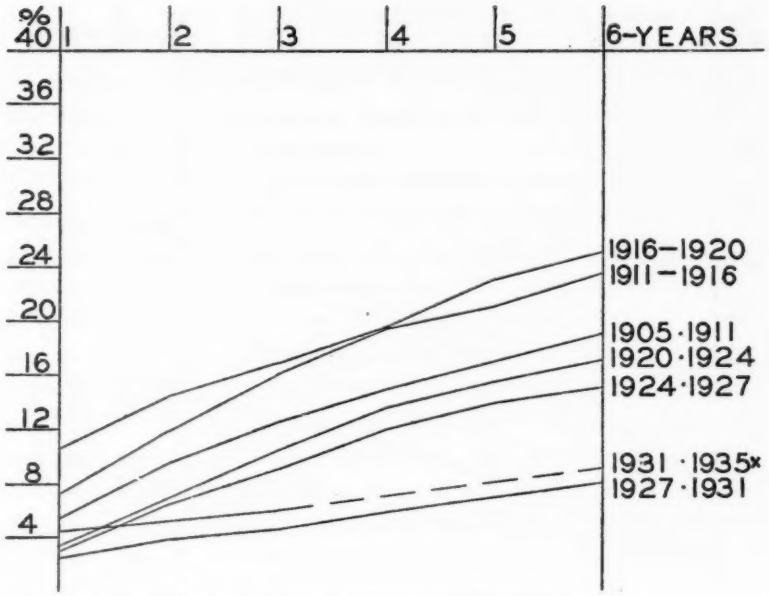

CHART 3. Accumulative death rate to six years for all groups.

* For group 1931–1935 the actual death rate is known for three to six years for all cases, and upon this basis the death rate for six years was computed.

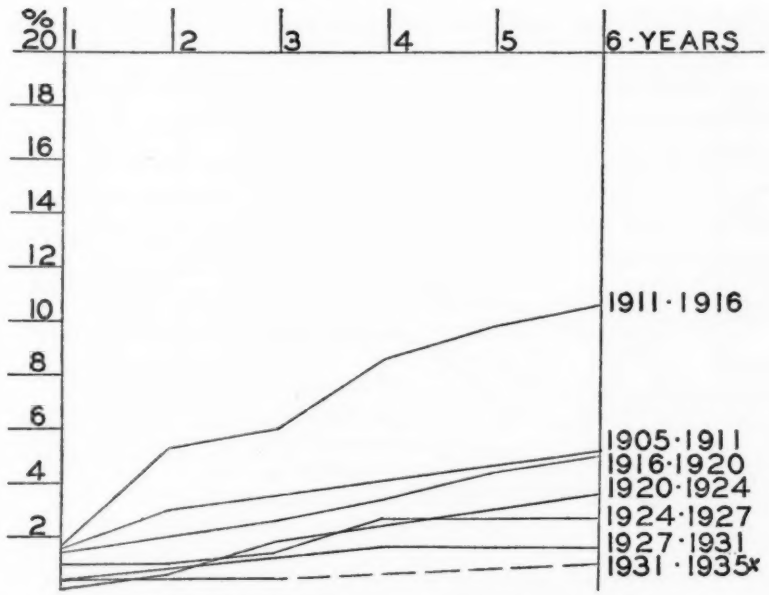

CHART 4. Accumulative death rate to six years—minimal cases—all groups.

* For group 1931–1935 the actual death rate is known for three to six years for all cases, and upon this basis the death rate for six years was computed.

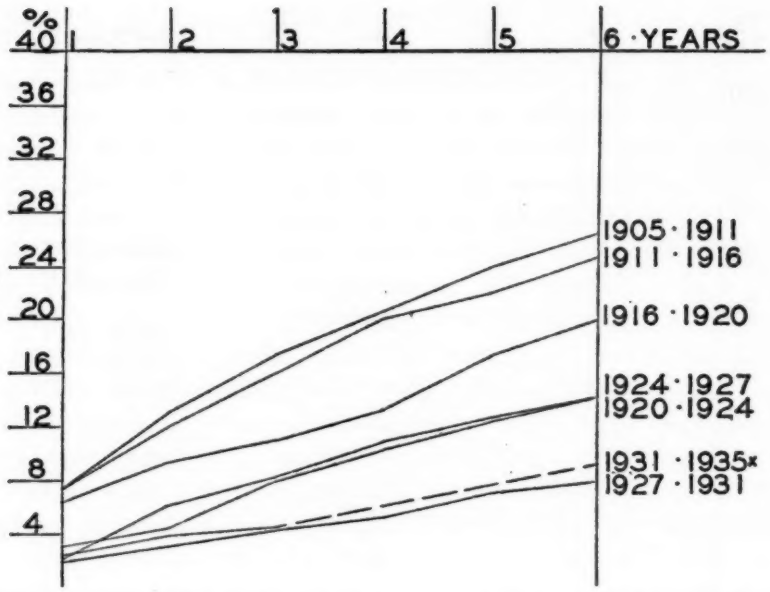

CHART 5. Accumulative death rate to six years—moderately advanced cases—all groups.
* For group 1931–1935 the actual death rate is known for three to six years for all cases, and upon this basis the death rate for six years was computed.

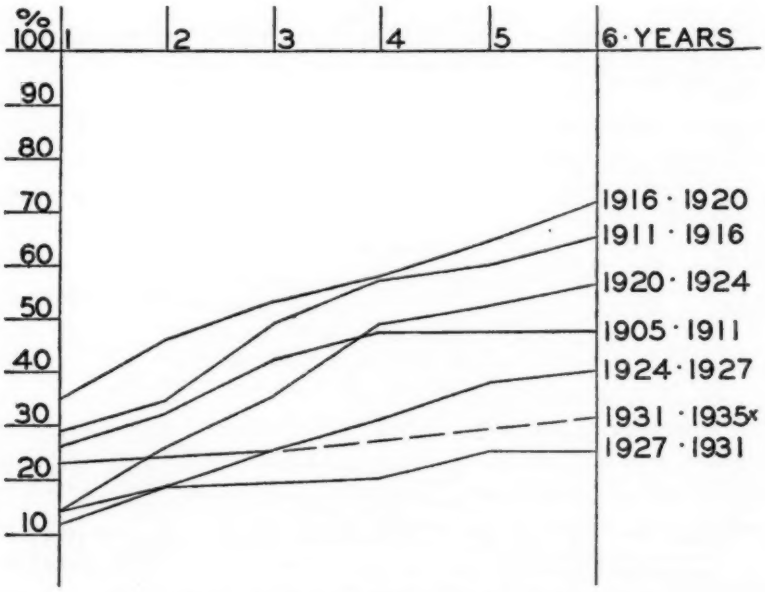

CHART 6. Accumulative death rate to six years—far advanced cases—all groups.
* For group 1931–1935 the actual death rate is known for three to six years for all cases, and upon this basis the death rate for six years was computed.

The method of treatment up to this time was the usual hygienic and dietetic procedure, although an occasional case (usually far advanced) did receive artificial pneumothorax.

The next (fourth) thousand cases covered a period between February, 1920 and February, 1924. It is necessary now to stop and consider for a moment two factors: (*1*) the roentgenogram was making itself felt in uncovering the disease earlier, and (*2*) we were beginning to appreciate the information revealed by the stereoroentgenogram. Ideas were crystallizing regarding shadows. Admittedly, this may be an empirical observation. However, in support of it, from this time on the number of nontuberculous cases entering Trudeau began to drop. It is also reasonable to assume that so-called "shadows" were better understood. The examining and staff physicians were undoubtedly using the roentgen evidence more profitably. As is the case to-day, some patients were slowed up or put to bed primarily upon the evidence of shadows seen in the roentgenogram.

In view of the fact that the roentgenogram played such an important part in the discovery of many of these cases, it is well to consider whether or not cases from this time on would differ in any way from those of the preceding groups. First, one might say that there is no reason to believe that they would. However, there is much to make one accept the statement that the tuberculosis of a goodly portion of this group was discovered much sooner than it would have been had no roentgenological examination been made. Hence, one is justified in saying this was a better group of cases. Either it was a better group of patients or the treatment was more effective, as will be shown by the following figures. (While there was a little greater sprinkling of the use of artificial pneumothorax in this group, it has no appreciable effect on the group as a whole, as not over 2 per cent received this treatment.)

Analysis of the Fourth Group

Nontuberculous 72 (7.2 per cent)
Suspect 45 (4.5 per cent)
Minimal 161 (16.1 per cent)
Moderately advanced 600 (60 per cent)
Far advanced 118 (11.8 per cent)

Several factors stand out very significantly in this group as compared with the previous groups. (*1*) There were almost twice as many far advanced cases in this group (11.8 per cent versus 6.5 per cent). (*2*) There were more cases of tuberculosis in this group, as the nontuber-

culous classification has fallen to 7.2 per cent, where in the preceding group it was 16.1 per cent. (*3*) The suspects number about the same as for the preceding group.

While the percentages for the classifications as to extent changed very little, later developments would lead one to believe that from this time on the roentgenogram became a much more valuable tool to use.

The death rate for this fourth group showed a marked decline in the group as a whole (17.8 per cent); in the separate classifications the rates were: minimal 4 per cent, moderately advanced 14 per cent, far advanced 55 per cent. As can be seen from charts 4 and 5, the death rate was about halved in the minimal and moderately advanced groups, as compared with group 2 (1911–1916). Why? It is recognized that far advanced cases are hard to save; nevertheless, the death rate for this group dropped 15 per cent as compared with the immediately foregoing group. Subsequent groups will confirm this decline. Again, we come back to the statement that either these latter were better cases of tuberculosis or the handling and understanding of the problems were more effectively applied.

Probably the only notes to be made on the fifth group (February, 1924 to August, 1927) are: (*1*) the death rate for the whole group fell to 15 per cent; (*2*) artificial pneumothorax was used in somewhat earlier cases. However, its use was very limited, as only 7 per cent received this form of treatment. Note should be made here that the death rate has fallen from 25 per cent in group 2 (1911–1916) to 15 per cent in group 5 (1924–1927).

An analysis of the sixth thousand cases (August, 1927 to January, 1931) revealed two points of interest. (*1*) Artificial pneumothorax was used more often (15.5 per cent as compared with 7 per cent). While most of the artificial pneumothorax treatment was started while the patients were at the sanatorium, some (a small percentage) had it applied after leaving. (*2*) The death rate for the whole group fell to 8 per cent. One might wonder whether this spectacular drop is just a "flash in the pan," and whether later groups will not reveal a return to former levels. Apparently not, as the death rate in the next (seventh) group (1931–1935) also is headed definitely toward a low level for the six-year period. (See chart 3.)

Analysis of this sixth 1,000-group reveals the following classifications (excluding nontuberculous and suspect cases): minimal 24 per cent, moderately advanced 57.2 per cent, far advanced 9.6 per cent. This

distribution, it will be noted, is very similar to that of the preceding group, with the exception that there is a larger percentage of minimal cases. This can be explained on the basis that fewer nontuberculous cases were admitted, a trend which, as stated above, is plainly seen since the use of the roentgenogram. Artificial pneumothorax was used at the sanatorium in about 15 per cent of the cases, distributed in the following manner: minimal 2.5 per cent, moderately advanced 15 per cent, far advanced 43 per cent. From this distribution it is obvious that artificial pneumothorax was used in a more or less limited fashion, but nevertheless twice as often as in the preceding group. Some sanatoria use this form of treatment in 80 per cent of their patients.

The death rate of 8 per cent for the whole group was divided in the different classifications as follows: minimal 2 per cent, moderately advanced 6 per cent, far advanced 25 per cent.

Put another way, a case of minimal tuberculosis had about a 50-to-1, a moderately advanced case about a 16-to-1, and a far advanced case a 3-to-1 chance of living six years. This obviously would be dependent upon proper treatment and after-care.

Before considering the next thousand cases, which brings us up to 1931–1935, it is well to examine the records which have to be beaten. The death rate in minimal tuberculosis has been reduced to almost an irreducible minimum (2 per cent at six years). Shall we arrive at that point where a case of minimal pulmonary tuberculosis has virtually no chance of dying of his disease within a specified time? This is not at all likely. Nevertheless, it may be said that the time when he may become a moderately advanced case has been appreciably extended.

Drolet's figures (1) would indicate that once pulmonary tuberculosis is well established (although he speaks for all pulmonary tuberculosis) the chance of dying of the disease is just as great to-day as it was twenty-five years ago. This can be questioned upon the basis that if the life of a case of minimal tuberculosis is prolonged sufficiently (and this is clearly demonstrated in the cases used in this study) these individuals live to die of other causes. Interesting in this respect is that up to the time this study is calculated (six years), minimal proliferative cases of tuberculosis die more frequently from nontuberculous causes than from pulmonary tuberculosis.

Our figures convince us that there has been a real decline in the death rate from pulmonary tuberculosis in the cases admitted to Trudeau during the past twenty years. Possibly this has been due in part to a

better selection of cases. Nevertheless, it can be said that other potent factors have helped materially to bring about this decline. A few of these may be mentioned: earlier diagnosis, more intensive education, better understanding on the part of the patient, more satisfactory home adjustment, better environment and food, coöperative attitude of industry, collapse therapy in selected cases.

The seventh thousand cases cover the period of time from January, 1931 to June, 1935. Again, there is a similar distribution of the classifications, namely, minimal 24.8 per cent, moderately advanced 57.6 per cent, and far advanced 11.6 per cent, or about the same as it was in the preceding group. Mention is made of this because of later statements.

So far all of these cases in the seventh group have not gone the full six years after discharge. However, all of them have passed the three-year milepost. The death rate at the present time, for three to six years postdischarge, is 8 per cent. With from one to three years to go on half of these 940 cases, it is quite probable that this rate will be raised to 9 or possibly 10 per cent for the six years. The actual death rate at three years for all the 940 cases was 6 per cent.

The fact that this group has in three to six years reached the 8 per cent death rate of the preceding group may be explained on the basis that a more advanced type of disease was present, or there may be other ways of explaining it.

A study of the predicted death rate curve for this group (see chart 3) indicates, as stated above, that the rate for the six years will be 9 or 10 per cent. Again, in this group the use of artificial pneumothorax was twice as frequent as in the previous group, 32 per cent as against 15.5 per cent. Also in this group an occasional patient had thoracoplasty. As a result of this more intensive collapse therapy, one would have expected the death rate to drop rather than to rise.

In order that we might make the figures more indicative, larger groups were compared. If one takes the two thousand cases between 1911 and 1920 (about ten years), and the last two thousand between 1927 and 1935, it will be seen that the death rate fell from about 24 per cent to 9 per cent. It seems reasonable to explain this through a combination of these factors: (*1*) the use of the roentgenograms in the latter group led to the discovery of the cases earlier than had been the case in the 1911–1920 period; (*2*) the roentgenograms enabled the physician to visualize the disease in shadow, thereby permitting a more effective

handling of the case; (*3*) the judicious use of collapse therapy, more particularly artificial pneumothorax.

Again, we can come back to the questions propounded at the beginning of this article: (*1*) Is the case of pulmonary tuberculosis to-day being recognized earlier? (*2*) Has a given case of pulmonary tuberculosis a better chance of recovery than the case of twenty-five years ago? And, again, the answer to each question appears to be "yes."

DISCUSSION

Several bits of information have been recorded by this study, and an effort will be made here to condense these so that the reader may "read as he runs."

If one will look at chart 2, it will be seen that in the two thousand cases between 1911 and 1920 there were fewer cases of pulmonary tuberculosis as compared with the two thousand cases between 1927 and 1935. Incidentally, the incidence of bacilli in the sputum was higher in the second group. This can be explained on the basis of better methods of finding them to-day. Now if one looks at chart 3, it will be seen that the death rate fell from about 24 per cent to about 9 per cent. This precipitous fall can hardly be looked upon as a drop that will rebound appreciably, because the curve that has already started for the next thousand cases is much the same as for this latter group.

It would seem safe to say that two factors were mainly responsible for bringing about this decline: (*1*) the advent of the roentgen-rays in the diagnosis and handling of the case; (*2*) the use of artificial pneumothorax (other forms of collapse had not made themselves felt as yet) supplementing the usual rest treatment.

While it is not seen in the accompanying charts, but is revealed in the so-called "wooden book," the division of cases into exudative and proliferative types has demonstrated where the greatest amount of collapse therapy was used. One illustration serves the purpose. In about 600 cases of moderately advanced disease, artificial pneumothorax was induced about five times, as often in the exudative as in the proliferative cases. In other words, it has been clearly demonstrated that more active treatment was apparently necessary in the exudative cases as compared with the more stabilized form of the disease, the proliferative. In this connection, the differentiation between the so-called exudative and the proliferative requires the best of stereoroentgenograms and extreme care in the interpretation.

Upon consulting chart 5, the death rate of the moderately advanced cases, it will be noted that the decline in the rate has been clearly shown over this thirty-year period. This observation is more impressive when one considers that the ratio of moderately advanced cases over this period of time hovered around 57 per cent for all groups.

CONCLUSIONS

1. The fatality rate of pulmonary tuberculosis at the end of six years has been steadily reduced in the patients of Trudeau Sanatorium.

2. The roentgenogram, facilitating earlier diagnosis and often the sole means of diagnosis, has played an important part, with other factors, in this decline.

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LARYNGEAL TUBERCULOSIS[1]

WILLIAM H. WEIDMAN AND HUGH B. CAMPBELL

After six years' experience with the electrocautery in the treatment of laryngeal tuberculosis an attempt has been made to summarize the results and to evaluate them. During this time we have been impressed with the lack of uniformity which exists in the treatment of the tuberculous larynx. Misconceptions are common and there is a wide range of opinions as to the effectiveness of various forms of treatment. The tuberculous larynx is frequently disregarded or is considered a very minor problem. At the other extreme laryngeal tuberculosis may be considered a very serious complication, which, when present, demands an unfavorable prognosis.

Because of this diversity of opinion we have frequently questioned the value of the therapy used at this institution. Cases, which in spite of all efforts failed to respond to treatment, at times convinced us that an unbridled enthusiasm for the use of the electrocautery had clouded our judgment. Confronted with this type of case, the limitations in the treatment of laryngeal tuberculosis are greatly magnified and the entire program is apt to be unjustly condemned. A study of this kind, however, brings into proper perspective the various details of this disease and tones down the more gruesome results. It becomes apparent that, in the presence of many therapeutic restrictions, there are some definite advantages which should be carefully utilized. There are failures; on the other hand, there are successes, and, if a conservative treatment is employed, the proportion of successes are more numerous.

Laryngeal tuberculosis varies in different institutions. The more prevalent the advanced case of pulmonary tuberculosis, the more likely is laryngeal tuberculosis to be a problem. Although this complication does occur in the minimal or moderately advanced case, it is much more frequent in the far advanced case. Those institutions in which there is a higher percentage of far advanced cases are more likely to be troubled by this problem. Whereas with a higher percentage of minimal or mod-

[1] From Uncas-on-Thames (State Tuberculosis Sanatorium), Norwich, Connecticut.

erately advanced cases, it is less prevalent and is, therefore, more apt to be misunderstood.

In this discussion unequally distributed vascular changes such as hyperaemia or anaemia, infiltrative thickening, oedema, tuberculomata or ulcerations occurring in the larynx of a patient with pulmonary tuberculosis are considered tuberculous. The posterior half of the larynx is usually the first to be involved, the order of frequency being the interarytenoid space, the arytenoids, vocal processes, cords, ventricular bands and the epiglottis. Only infrequently is the anterior commissure the original site. Congestion is the earliest change noted and may rapidly or slowly develop into an infiltrative thickening or ulceration. Perichondritis and necrosis are terminal changes and are commonly quite difficult to treat. An acute catarrh, reddened irregular swelling of the interarytenoid mucosa, papillary formation in the same area, roughness and thickening of the vocal cords occurring in a patient with pulmonary tuberculosis indicate laryngeal tuberculosis. Later there may be ulcerations or tuberculomata; all these changes may be present at the same time.

No attempt has been made to classify the laryngeal cases into groups of acute, subacute or chronic. For all practical purposes this is quite useless. It is much more profitable to study the associated pulmonary lesions, for it is here that the fate of the larynx is determined.

It is inadvisable to wait until symptoms develop before an examination of the larynx is made. Early laryngeal involvement is relatively common and unaccompanied by symptoms. Frequently it remains unsuspected until discovered in a routine examination. It is astonishing at times to find marked laryngeal ulceration and oedema without associated symptoms other than hoarseness if the vocal cords happen to be involved. Every tuberculous patient irrespective of the extent of the pulmonary lesion should have a laryngeal examination. Furthermore, frequent reëxaminations should be done on those whose pulmonary lesion remains uncontrolled. Many of the cases included in this series had a normal larynx on admission. Had reëxamination been neglected, a large group would have remained undiscovered. It must be remembered that laryngeal pain is a late symptom and if its presence is awaited before diagnosing laryngeal tuberculosis valuable time is lost.

It is difficult to distinguish a simple catarrh, syphilis and carcinoma from laryngeal tuberculosis. The following case clearly demonstrates this point.

A male, age 63, was admitted to this institution June 3, 1936, from the New Haven Hospital. There was evidence of an active pulmonary tuberculosis involving both upper lobes with cavity formation in the right upper lobe. Pneumothorax of two months' duration had failed to collapse the right apical cavity. Sputum examination at the time of admission was negative, although it had been positive the previous March. Laryngeal examination on June 4, 1936, revealed an oedema of the left arytenoid, on the face of which was a small area of necrosis containing a yellowish exudate. On July 2, 1936, the eft arytenoid was markedly oedematous and an infiltrative thickening extended upward onto the posterior surface of the epiglottis. The lesion was cauterized but gradually became worse. In September there was a large fungoid mass involving the left half of the epiglottis and the arytenoid. The surface of this mass was ulcerated and showed a sticky yellowish-green exudate on its surface. A belated diagnosis of carcinoma of the larynx was made. After consultation with a laryngologist it was thought that the pulmonary lesion, which had extended during this time, precluded any operative interference. An autopsy performed in January, 1937, confirmed the diagnosis of laryngeal carcinoma.

This case is presented in some detail to demonstrate the difficulties encountered in the diagnosis of laryngeal tuberculosis. There is frequently such a similarity between tuberculosis and carcinoma that one is apt to be unduly influenced by the presence of an active pulmonary tuberculosis.

In July, 1936, 25 patients who showed laryngeal tuberculosis by indirect laryngoscopy were X-rayed in an attempt to evaluate the use of X-rays for the diagnosis of laryngeal tuberculosis. The technique used was as follows: 960 MA., $\frac{1}{60}$ sec., 60 KV., at a 6 foot distance. It was found that gross changes were clearly visible. Early lesions, however, such as congestion and slight infiltrative thickening could not be detected. Considering the cost of this procedure, the results obtained did not seem to warrant its continuance. Indirect laryngoscopy is considered to be superior. The use of the X-ray may be of value in those cases where it is impossible to visualize the larynx by any other means.

The presence of laryngeal tuberculosis may or may not have an effect on the prognosis of a patient with pulmonary tuberculosis. In those cases where the pulmonary lesions can be controlled laryngeal tuberculosis plays a relatively unimportant part in the prognosis. With the improvement of the patient the laryngeal involvement gradually assumes chronicity and eventually heals. If cauterization is not resorted to, the laryngeal tuberculosis may persist for an unnecessarily long time,

but the ultimate cure is not prevented, it is merely delayed. If, however, in these cases the laryngeal involvement is so extensive that there is continued difficulty in eating, the pulmonary lesion will not respond to treatment as it should. In those cases showing pulmonary chronicity and in which there is no hope for its ultimate control the duration of the illness can be lengthened by satisfactorily controlling the laryngeal complication. In the retrogressing case, if the laryngeal symptoms remain unalleviated, the individual succumbs more rapidly than in a similar case without laryngeal disease. Occasionally laryngeal tuberculosis is so acute that death is almost attributable to it. Fortunately this fulminating type of laryngeal tuberculosis is infrequent.

A survey of the patients admitted to this institution from 1932 to 1937, inclusive, has been made. During these six years 2,186 patients were under care in this institution. In order to obtain a fairly accurate figure, all cases of lung abscess, pulmonary neoplasm and bone tuberculosis without pulmonary involvement were excluded. Readmissions, irrespective of the number of times admitted, were considered as one case. In this manner, 370 patients have been excluded and the remaining 1,816 were used in this survey of which there were 918 males and 898 females. Four hundred and sixty-eight of the 1,816 cases, or 26 per cent, had tuberculous laryngitis. It was found that 269 males, or 30 per cent, had laryngeal tuberculosis, while in the females this complication was less frequent, there being 199, or 22 per cent.

It is felt that the incidence of laryngeal tuberculosis is greater than these figures would indicate. It is impossible to follow all cases of pulmonary tuberculosis from inception until the individuals succumb to it. Arrested cases may subsequently retrogress without coming under observation. An indication of the validity of this reasoning is suggested in the readmissions to this institution. At least one-quarter of the patients, who on the first admission had a negative larynx, subsequently developed this complication.

The age of this group (chart 1) varied from fifteen to seventy-three years; 6 men were over seventy years of age, while sixty-five was the highest age attained by the women; 68 per cent of the females were in the age group between sixteen and thirty years; whereas 79 per cent of the males were between twenty-one and fifty years. This age grouping is not considered characteristic of laryngeal tuberculosis. It merely represents the usual grouping noted in a sanatorium of this type. We all recognize the preponderance of the female as compared to the male in the

lower age group. In the older age group, laryngeal tuberculosis is relatively more frequent, not because of any characteristics of laryngeal tuberculosis, but for the reason that the longer pulmonary tuberculosis remains uncontrolled, the more apt is this complication to occur.

The question arises as to the existence of a primary laryngeal infection. Unfortunately it is impossible for us to definitely deny this possibility. Inasmuch as our experience is confined to patients with pulmonary

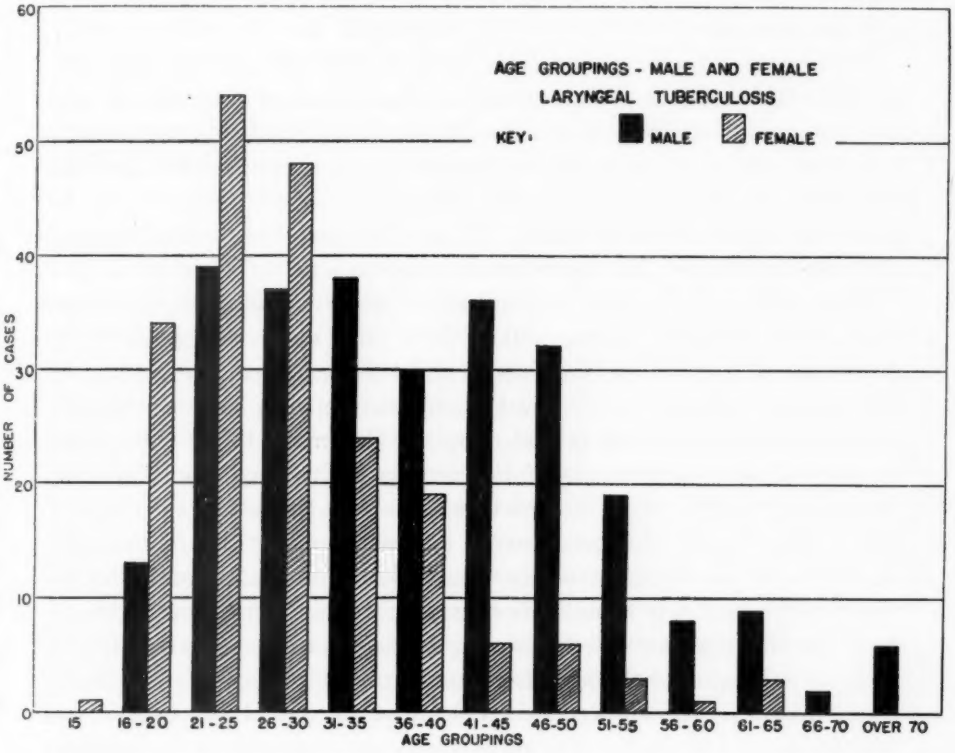

CHART 1

tuberculosis, a primary laryngeal tuberculosis would not be brought to our attention. However, in this group there were 27 cases, or 5.6 per cent, with persistently negative sputa while under our observation. In all these cases a routine examination was made on four separate specimens of sputa. A further examination was made on concentrated specimens planted on Petroff's media. Unfortunately there were no guinea pig inoculations done. However, in spite of the negative sputa, a definite

diagnosis of pulmonary tuberculosis seemed warranted from the history, the physical examination and X-ray findings. In quite a few of these cases a previous history of a positive sputum was obtained. These statements could not be confirmed by our examination. Although the existence of a primary laryngeal tuberculosis cannot be denied, it seems to be a much wiser diagnostic procedure to forget its remote possibility. The similarity of other diseases to laryngeal tuberculosis is often so marked that an X-ray examination of the chest should be available as a diagnostic aid.

During the six-year period from 1932 to 1937, 50 patients were admitted with a positive Wassermann, 41 cases of silico-tuberculosis, and 50 cases complicated by diabetes mellitus. Laryngeal tuberculosis was a further complication in six, or 12 per cent, of those with a positive Wassermann; 10, or 24.3 per cent, with silico-tuberculosis; 12, or 24 per cent, with diabetes mellitus. In each instance the total number of cases are considered too small for any conclusions to be drawn.

Five cases, or 1 per cent, had oral tuberculosis complicating the laryngeal and pulmonary lesions. All of these cases died. One male, fifty-five years of age, showed carcinoma and tuberculosis of the dorsum of the tongue. Another male, thirty-four years of age, had tuberculosis of the tongue on the left lateral margin. One male, thirty-eight years of age, showed tuberculosis of the tongue at its tip. Another male, forty-three years of age, showed tuberculosis of the left labial commissure. One female, nineteen years of age, with miliary tuberculosis had an extensive involvement of the uvula, soft palate and tonsils. Oral tuberculosis is a rare complication as seen in this institution and inasmuch as all these cases died this complication can be considered serious. It is an indication of the serious extent of the pulmonary lesion. However, the male who showed tuberculosis at the tip of the tongue was hospitalized 1,762 days. The tuberculous ulcer apparently healed after cauterization and heliotherapy. It was impossible to control the patient's pulmonary lesion even though its chronicity was evident; he eventually died. All these cases of oral tuberculosis were confirmed either by biopsy or from pathological examination after autopsy.

It was very surprising to find that, with all the operative interference on the larynx during this period, only 2 cases of laryngeal oedema were encountered. In neither case was cauterization the cause. One case occurred in a girl twenty-eight years of age soon after admission. Laryn-

geal tuberculosis was present at the time of admission but did not appear to be extraordinary in its extent or character. Speech was not markedly impaired at the time of the first examination. In a few days hoarseness became progressively worse until there was a sudden marked dyspnoea. The dyspnoea was acute in onset and necessitated a tracheotomy. Although the laryngeal oedema gradually subsided, the patient's pulmonary condition progressed and she died within three months' time. The other case, occurring in a girl twenty-four years of age, was a terminal phenomenon. It was gradual in onset and progression, involving all the structures of the larynx.

The question has frequently arisen as to what part the tonsil plays in the development of laryngeal tuberculosis. In 400, or 85.5 per cent, the tonsils were present. They were absent in 68, or 14.5 per cent. In a group of patients selected at random with pulmonary tuberculosis but without laryngeal tuberculosis, 387, or 82.5 per cent, had tonsils, while in 81, or 17.5 per cent, tonsils were absent. It was impossible to select a group with identical pulmonary involvements, but in the selection made there was a high percentage of far advanced cases. It is felt that the tonsils play no obvious part in the development of laryngeal tuberculosis since the percentage difference in the two groups is so small.

All patients on admission were given a laryngoscopic examination. If the larynx was normal and the pulmonary tuberculosis remained uncontrolled, the larynx was reëxamined at two-month intervals unless laryngeal symptoms developed in the interim. The frequency with which laryngeal tuberculosis developed subsequent to admission was surprising. Because of the frequent absence of symptoms, many cases would have remained undetected or would have reached alarming proportions if periodic examinations had not been made.

As soon as laryngeal tuberculosis was diagnosed, the patient was placed on vocal rest. If with the general regimen, or collapse therapy, the larynx improved, nothing more was done. Irrespective of the treatment of the pulmonary condition all patients whose larynx showed a congestion or slight infiltrative thickening were treated with vocal rest alone. If, however, oedema or ulceration were present, the larynx was cauterized, providing the general condition of the patient permitted. The larynx which shows only congestion should never be cauterized. Only those showing stages more advanced than congestion or infiltrative thickening were considered suitable for cauterization.

It must be stressed that irrespective of the laryngeal condition its treatment is directly dependent upon the pulmonary conditions. The following example is presented.

A male, 35 years of age, was admitted to this institution with a far advanced pulmonary tuberculosis involving both lungs completely with cavity formation in the left upper lobe. There was an evening rise of temperature to 100° or 101°F. His voice was hoarse, cough was painful and there was a marked dysphagia. The prognosis of the case was poor and it was felt that he would die within a relatively short time. The larynx showed marked oedema of all the structures with ulceration of the ventricular bands and cords. The relief of laryngeal pain seemed to be the most desirable treatment and, accordingly, the superior laryngeal nerve was injected bilaterally with excellent results. The patient was able to eat and within a comparatively short time he was considered a fit subject for pneumothorax treatment. Pneumothorax was instituted on the left side and there was a gradual improvement in his general condition. The larynx, in the meantime, had improved somewhat although ulceration and oedema were still present. The larynx was cauterized and subsequently there was a rapid improvement in both the laryngeal and pulmonary symptoms.

The use of the cautery can be greatly abused if certain facts are ignored. The groups most amenable to this form of treatment are well defined. It is inadvisable to cauterize the larynx which shows only congestion, and it is absolutely useless in an acute laryngeal tuberculosis occurring as a terminal complication. Cauterization of the larynx of the patient whose pulmonary prognosis is hopeless is inadvisable, providing, of course, that there is fever and his condition is retrogressing. The cautery is of great value in that group which shows chronicity or improvement. It must be understood that there are many patients with a hopeless prognosis who remain in the sanatorium a considerable length of time before dying. It is in this latter group that the real value of cauterization is evident.

Patients developing laryngeal tuberculosis have on the whole a very poor prognosis to begin with. Of the 468 patients included in this series 408, or 87.2 per cent, were classified as far advanced cases on admission, 3 of these being miliary in type. There were 53, or 11.3 per cent, moderately advanced cases and 7, or 1.5 per cent, minimal. The grouping of the pulmonary involvement at the time of admission does not give an accurate picture, for many of the cases classified as moderately advanced progressed to the far advanced stage while in the sanatorium, as did two

cases which were first classified as minimal. In the latter instance there was an associated tracheobronchial tuberculosis which remained uncontrolled and ultimately caused death. It is unfortunate that it was impossible to study the correlation of laryngeal tuberculosis with the presence of a tracheobronchial ulceration. However, we have noted in some cases brought to autopsy, in whom it was impossible to control the pulmonary or laryngeal tuberculosis, that there was extensive tracheobronchial ulceration. In these cases cauterization of the larynx proved ineffectual. It appears quite clear from the foregoing, considering the high percentage of far advanced cases, that any successes obtained in the treatment of the pulmonary or laryngeal lesions may be regarded as salvage.

The results of the treatment of laryngeal tuberculosis are so intimately associated with the treatment of the pulmonary lesion that it is almost impossible to properly evaluate the results, for example:

One case comes to mind in which there was a large tuberculoma of the interarytenoid mucosa in a patient with far advanced bilateral pulmonary tuberculosis. The gag reflex in this individual was so active that it was practically impossible to examine the larynx, let alone cauterize it. The patient received pneumothorax and later a thoracoplasty was done with the result that the sputum became negative and the larynx gradually healed. This case clearly demonstrates the importance of collapse therapy in the treatment of laryngeal tuberculosis.

Table 1 is an attempt to clarify this relationship; 322, or 69 per cent, patients were treated with vocal rest alone; 139, or 43.2 per cent, showed satisfactory results; 35, or 10.8 per cent, were considered partially satisfactory; 126, or 39.2 per cent, were unsatisfactory; 15, or 4.6 per cent, received insufficient treatment, while in 7, or 2.2 per cent, the larynx was not treated. These patients were then classified according to the effectiveness of the collapse therapy whenever employed and also according to the results obtained without collapse therapy. It appears evident (table 1) that there was a high percentage of favorable laryngeal results in those cases whose pulmonary tuberculosis responded satisfactorily to sanatorium treatment irrespective of the type. It is also evident that a higher percentage of satisfactory laryngeal results were obtained in the group responding to collapse therapy. In the group showing 35 partially satisfactory laryngeal results there is a shift of the effectiveness of the collapse therapy to the unsatisfactory group. In considering the un-

TABLE 1

Laryngeal tuberculosis—results of treatment

PULMONARY CONDITION ON DISCHARGE	CAUTERIZED CASES				VOCAL REST CASES					TOTAL CASES				
	Satisfactory	Partially satisfactory	Unsatisfactory	Insufficient treatment	Satisfactory	Partially satisfactory	Unsatisfactory	Insufficient treatment	No treatment	Satisfactory	Partially satisfactory	Unsatisfactory	Insufficient treatment	No treatment
Collapse therapy														
Satisfactory	27	4	0	0	83	2	0	0		110	6	0	0	
Partially satisfactory	7	4	0	0	26	8	0	0		33	12	0	0	
Unsatisfactory	15	25	19	1	8	11	33	3		23	36	52	4	
No collapse therapy														
Satisfactory	4	1	0	0	4	0	0	0		8	1	0	0	
Partially satisfactory	5	3	0	0	13	6	0	0		18	9	0	0	
Unsatisfactory	2	8	19	2	5	8	93	12		7	16	112	14	
Number of cases	60	45	38	3	139	35	126	15	7	199	80	164	18	7
Per cent of cases	41.0	31.0	26.0	2.0	43.2	10.8	39.2	4.6	2.2	42.6	17.1	35.0	3.8	1.5
Discharge sputum (number and percentage)														
Positive	24 40.0%	38 84.5%	38 100.0%	3 100.0%	26 18.7%	28 80.0%	125 99.2%	15 100.0%	7 100.0%	50 25.1%	66 82.5%	163 99.4%	18 100.0%	7 100.0%
Negative	36 60.0%	7 15.5%	0	0	113 81.3%	7 20.0%	1 0.8%	0	0	149 74.9%	14 17.5%	1 0.6%	0	0

satisfactory laryngeal results, this relationship is very clearly demonstrated, for in the group of 126 unsatisfactory laryngeal results both the ordinary sanatorium regimen and collapse therapy proved ineffectual in halting the progress of the pulmonary lesion. The relationship of the results of the sputum examination has been correlated with the laryngeal results and these figures are interesting in that they demonstrate the importance of controlling the pulmonary lesion. In the group showing satisfactory laryngeal results, the sputa of 113, or 81.3 per cent, were negative. In the partially satisfactory laryngeal results the frequency with which positive sputa occurred became greater. In the unsatisfactory laryngeal group 125, or 99.2 per cent, examinations were positive at the time of discharge. The one negative sputum examination in this group is probably inaccurate, for this particular patient died of an acute tuberculous pneumonia with an associated laryngeal tuberculosis.

In 146, or 31 per cent, the larynx was cauterized. Cauterization was done anywhere from one to eight times on each patient, there being a total of 240 cauterizations. The results are shown in table 1. It will be noted that the same relationship exists between the results of the treatment of the pulmonary lesion and the results obtained by cauterization of the larynx as compared to the group treated with vocal rest alone. Much better laryngeal results were obtained when the pulmonary lesion responded to treatment. There were these exceptions however: 72 per cent of the group receiving cauterization showed satisfactory or partially satisfactory laryngeal results; whereas in the group treated with vocal rest alone this percentage was 54. This difference is accounted for by the high percentage of partially satisfactory cauterizations. There was also a higher percentage of satisfactory laryngeal results with positive sputa at the time of discharge in the cauterized group. In the satisfactorily cauterized cases 40 per cent showed positive sputa, as compared to 18.7 per cent positive in the vocal rest group. The remaining results of the sputa are too similar to be of interest.

The comparison of the satisfactory results in the cauterized and uncauterized groups with relation to the pulmonary results is interesting. In 43, or 71 per cent, of the satisfactory results from cauterization the pulmonary lesion responded wholly or in part to treatment and in 17, or 29 per cent, it retrogressed. In the uncauterized group 126, or 90.6 per cent, had favorable or partially favorable results from the pulmonary treatment, whereas in only 13, or 9.4 per cent, did the larynx improve as the pulmonary lesion retrogressed. This paradox is occasionally

noticed when there is congestion or a slight infiltrative thickening of the larynx. Improvement follows strict vocal rest and control of the cough.

It is unfair to compare the results of cauterization with those of vocal rest alone for these reasons: in the first place, whether a larynx was cauterized or not, the patient was placed on vocal rest; in the second place, as shown in table 2, 90.4 per cent of the patients receiving laryngeal cauterization were far advanced cases, whereas in the vocal rest group they were 85.7 per cent. Another difference is that the patients receiving vocal rest consisted of two groups. In one there were those cases whose prognoses were good and who responded to ordinary sanatorium regimen. In the other there were those whose pulmonary prognoses were too poor to warrant cauterization of the larynx. It is very difficult to prove statistically the value of laryngeal cauterization. There are too many factors which cannot be definitely determined.

TABLE 2

Pulmonary involvement on admission

PULMONARY INVOLVEMENT ON ADMISSION	CAUTERIZED 146 CASES—31.0%		VOCAL REST 322 CASES—69.0%		TOTAL 468 CASES—100.0%	
	Number	Per cent	Number	Per cent	Number	Per cent
Far advanced	132	90.4	276	85.7	408	87.2
Moderately advanced	13	9.0	40	12.4	53	11.3
Minimal	1	0.6	6	1.9	7	1.5
Total	146	100.0	322	100.0	468	100.0

Considering this problem impartially, there appears to be a definite benefit resulting in the judicious use of the cautery. It must be remembered that the extent of the pulmonary involvement determines in a large measure the results of the laryngeal treatment obtained; for example, 53 cases classified as moderately advanced at the time of admission showed 75.5 per cent satisfactory laryngeal results irrespective of the laryngeal treatment.

At the completion of this survey in July, 1938, the pulmonary condition of this group at the time of discharge was as follows: 199, or 42.5 per cent, died; 47, or 10 per cent, were unimproved; 65, or 13.9 per cent, were still in the sanatorium; 101, or 21.6 per cent, showed improvement; 34, or 7.3 per cent, were quiescent; while 22, or 4.1 per cent, were considered to be arrested. From the foregoing it is evident that the group of laryngeal cases at the time of admission had a poor prognosis and the

percentage of favorable results in the treatment of the pulmonary lesion was not predominant.

It must be understood that cauterization of laryngeal tuberculosis will not in itself relieve pain. Pain may be relieved by cauterization in those cases in which the pulmonary disease responds to treatment or at least shows chronicity. In those cases which do not respond to treatment or in which the laryngeal as well as the pulmonary involvement progresses, pain is a very disheartening symptom to control. It may be controlled somewhat by the ingestion of powdered acetyl-salicylic acid or by spraying the larynx with a 2 per cent to 4 per cent cocaine solution. Usually in the cases where pain is predominant the epiglottis and arytenoids are markedly oedematous and ulcerous. If these minor procedures prove ineffectual, some relief might be obtained by injecting the superior laryngeal nerve. The nerve is first injected with 0.5 cc. of novocaine solution immediately followed by 0.5 to 1 cc. of 95 per cent alcohol. This procedure in itself is at times very painful, but less pain is produced when the amount of injected alcohol is kept at a minimum. When too large a quantity is used, the alcohol tends to spread between the fascial spaces and so produces pain in the tongue or occasionally in the lower teeth. The injection of the superior laryngeal nerve can be classified as a "hit or miss" procedure. It is sometimes difficult to locate the nerve and frequently, even after it has been located and injected, the anaesthetic effect may be transitory, varying anywhere from a few days to a few months. At times, even though the injection is satisfactorily performed, there is persistent difficulty in swallowing, accompanied by an agonizing pain. Recently Stott (1) has advocated multiple nerve blocking for relief in this type of pain. Our lack of sufficient experience with this procedure precludes any criticism. However, the cases requiring nerve blocking at this institution often refuse the extensive manipulation which this procedure requires.

Previous to the introduction of cauterization at this institution many other forms of laryngeal therapy had been used varying from the use of chaulmoogra oil to heliotherapy. Certainly laryngeal cauterization combined with vocal rest has produced the most satisfactory results, even though its limitations are recognized. If the use of the cautery is not too enthusiastic and its limitations are frankly admitted, its value appears to be unquestionable. There have been no serious complications such as laryngeal oedema or haemorrhage encountered in its use. Oedema and haemorrhage do occur, however, when the larynx is cauter-

ized too extensively. Our procedure has been to cauterize frequently rather than extensively and never cauterize the same area at intervals of less than six to eight weeks. The epiglottis is less likely to produce laryngeal oedema when cauterized and for that reason can be more extensively cauterized than the cords or arytenoids.

SUMMARY

Irrespective of treatment the results in laryngeal tuberculosis were, as follows: there were 468 patients with laryngeal tuberculosis and in 199, or 42.6 per cent, satisfactory results were obtained; 80, or 17.1 per cent, showed partially satisfactory results; in 164, or 35 per cent, the results were unsatisfactory; 18, or 3.8 per cent, received insufficient treatment and 7, or 1.5 per cent, were not treated.

It seems quite evident that with the high percentage of unsatisfactory results in the treatment of laryngeal tuberculosis there is much to be desired. Although laryngeal cauterization, combined with the sincere effort to bring the pulmonary condition under control by the judicious use of all forms of collapse therapy, has definite value, there still remains a large group of patients in which laryngeal treatment is ineffective. This problem is not directly the problem of the treatment of laryngeal tuberculosis. It only demonstrates that there is as yet no certain cure for pulmonary tuberculosis.

We are indebted to Dr. Edward J. Whalen of Hartford, Connecticut, for his instruction on the proper use of the electrocautery.

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PRESERVATION OF TUBERCLE BACILLI[1]

MAURICE L. COHN

Only a decade ago, the problem of maintaining strains of tubercle bacilli over long periods of time resolved itself into the making of new transplants at intervals of eight weeks to six months (1). If kept for longer intervals, these cultures often proved unsatisfactory for accurate study. The inability to obtain transplants from the ordinary solid media, such as gentian violet egg medium and glycerol broth agar, was due to the fact that small amounts of static dyes, the hypertonicity of the drying medium, as well as the natural accumulation of detrimental materials from the bacilli themselves, all acted destructively upon the bacilli. This was more evident in 1933 when Corper and I (2) reported on the maintenance of viability and virulence in twelve-year old broth cultures of human and bovine tubercle bacilli kept at incubator temperature. This was the longest recorded time of the preservation of individual strains of tubercle bacilli in cultures, and this method was suggested for such purpose and used with success. Maintaining water and air balance and at the same time avoiding evaporation of the broth possessed advantages unattainable by other means, but the large bulk of liquid and bacillary mass made this method disadvantageous under certain circumstances, especially as space-consuming and not readily transportable. However, these studies showed that tubercle bacilli could remain alive for a considerable time under suitable circumstances and that they could be compared with their progeny if desired. The same year (1933) Harris and Lange (3) in a two-page report published the results of using a modified Brown's method for preserving tubercle bacilli *in vacuo*. Essentially, the method used was as follows: "kernels" of a young culture were transferred to vials and the vials placed over calcium chloride in one-half to one pint bottles. The bottles were evacuated under a bell jar until a high vacuum was obtained by a water pump (? pressure) then capped by a hand crimping machine. Thirty-one strains of acid-fast bacilli (tubercle bacilli and saprophytes) from Petroff and Lubenau media were used (four-week old cultures). The

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

"kernels" were examined after eleven months' storage in the refrigerator. In forty-eight hours, all the saprophytes had grown. In three weeks, most of the pathogens had grown, which indicated that all the acid-fast bacilli had remained alive up to the interval tested (eleven months at refrigerator temperature). Although this study showed that lumps of acid-fast saprophytes and tubercle bacilli could remain alive for all practical purposes for eleven months in a stoppered receptacle with probably a poor grade vacuum and partial drying, there were many points of information needing further elaboration for the purpose at hand, especially since ordinary cultures of acid-fast saprophytes and tubercle bacilli can remain viable at incubator temperature for this length of time if proper precautions are taken against the action of antiseptic dyes or drying.

In a valuable academic study, Potter (4) in 1935 showed that avian tubercle bacilli survived at 37°C. a registered initial vacuum of one-billionth of an atmosphere for over eight months and oxygen deprival for over eighty days, which was associated with extensive desiccation essential to the methods of oxygen removal. The water loss of the bacilli was not actually determined but must have been as complete as chemically obtainable, nor was the number of viable organisms noted. In 1937, Potter (5) reported on additional experiments with the same strain of avian tubercle bacilli, maintained at room temperature, and found them to be viable after fourteen months and two years respectively of exposure to a "high vacuum, oxygen deprival and severe desiccation." These experiments were of great value in showing that at least one strain of pathogenic tubercle bacilli (avian) could survive extreme conditions of vacuum, drying and oxygen deprival for two years.

Among recent articles on the preservation of bacterial cultures is one (1938) by Morton and Pulaski (6) who, though dealing with rapidly growing organisms, bring up many points that must be considered for the storage of all microörganisms. In a valuable bibliographic review of the literature, they point out that, in order to preserve cultures and at the same time to maintain them in as nearly as possible their original state, two principles appear to be involved: first, the prevention of slow-drying of the cultures, and second, the use of rapid desiccation. The literature reveals that most of the methods of preservation have been tried only on a limited number of bacterial species; practically none have been subjected to critical study. Finally, three representative methods were considered worthy of test for most of the species commonly main-

tained by teaching laboratories. One of these, perhaps the first attempt to preserve cultures, consisted of sealing the end of the tube containing the actively growing organisms (such storage of broth cultures in ampoules did not prove wholly satisfactory and was not suited for many species). The second method is noteworthy in that it attempts not only to preserve the cultures but also to keep them readily available for multiple transplantations (the authors found that properly prepared oil covering possesses many distinct advantages over the first method). In contrast to the first two methods, the third method employs the principle of rapid desiccation (slow desiccation in air appears to have a decidedly lethal effect) which has the advantage that (*a*) less space is required for storage, (*b*) the cultures are more easily transported, and (*c*) certain immunological properties are maintained. The disadvantages of the rapid desiccation method are the cost of special equipment for the ordinary laboratory and the time and effort necessary when large collections are being preserved. For the latter reasons, the authors are partial to the oil method, although they intend to report more fully in additional studies on the rapid desiccation method, which is being elaborated further. Although they studied a wide variety of microorganisms and obtained valuable information on these, no tubercle bacilli were included.

Since earlier tests showed that well grown cultures on glycerol broth, properly protected against evaporation, could still contain viable human and bovine tubercle bacilli without loss of original virulence for over twelve years at incubator temperature, and since the use of methods of hermetic sealing or of oil covering introduced definite technical disadvantages for the storage of mammalian tubercle bacilli, and because we were interested in studying the effects of certain other gases besides air upon the preservation of these bacilli, our experiments were conducted to solve some of these problems as well as to elaborate upon the rapid desiccation studies of Harris and Lange, and Potter in quantitative tests.

EXPERIMENTAL

In all of the following experiments, the viability of tubercle bacilli was determined quantitatively by planting known graded quantities, from 1 mg. to 0.000,001 mg. of fine bacillary suspension, on a delicate medium (the glycerol water egg yolk medium previously described and standardized by us (7, 8)). In the first experiment, small amounts (50 to 100 mg.) of young (three weeks old) well grown cultures of human,

bovine or avian tubercle bacilli taken from tubes on inspissated broth whole egg medium were aseptically transferred to sterile vials. Some vials were sealed in the flame immediately, some were drawn to a capillary constriction and then placed in a vacuum desiccator containing phosphoric anhydride; after drying for three days, the tubes were sealed rapidly by a flame (in some of the earlier experiments the tubes were protected against absorption of moisture while sealing by means of an attached calcium chloride tube). Analysis for water content of these bacilli showed a loss of 73.7 per cent weight for the virulent human (H7) tubercle bacilli, 76.8 per cent for the avirulent human tubercle bacilli, 70.6 per cent for the virulent bovine tubercle bacilli, and 72.1 per cent for the avian tubercle bacilli. Where oxygen or nitrogen was used for filling the vials, they were drawn down to a fine capillary constriction and attached to a manifold which was evacuated with a water pump down to a vacuum of 17 mm. pressure of mercury and allowed to fill with the gas used, oxygen or nitrogen. The process was repeated three times, and finally the vial was sealed under slight vacuum to avoid blowing out of the vial during heat sealing. All the vials were protected from light by keeping them in a sealed can with black lining. The effects of storage of the desiccated and nondesiccated (natural) bacilli at incubator (37°C.), room (20°–30°C.) and refrigerator (3°C.) temperatures upon their viability after six months to three years are recorded in tables 1 and 2.

The results recorded in table 1 indicate that the strains of avirulent and virulent (H7) human tubercle bacilli desiccated and preserved in a sealed tube retained their viability almost completely (to the .000,001 mg. dilution) for one year at refrigerator temperature and down to the 0.000,1 mg. dilution after three years; while at incubator temperature, loss of viability was complete within one year and markedly diminished within six months; at room temperature, although the loss of viability was perceptible at six months, some of the bacilli were still alive after one year, but loss of viability was complete after two years with both human strains of tubercle bacilli. The nondesiccated sealed tubes always showed an earlier loss of viability of the human tubercle bacilli, even at refrigerator temperature, although survival was good up to one year.

The virulent strain of bovine tubercle bacilli tested (see table 2) showed a poorer survival in nondesiccated form at room and incubator temperature than the human tubercle bacilli; but it survived beyond the three-year limit in desiccated form at refrigerator temperature to the 0.000,001 mg. dilution, showing that most of the bacilli under these

TABLE 1

Effect of storage upon the viability of natural and desiccated tubercle bacilli

STRAIN OF BACILLI (FROM INSPISSATED WHOLE EGG BROTH MEDIUM)	TIME INTERVAL	STORAGE TEMPERATURE	AMOUNT OF SUSPENSION IN MG. PER CC. USED FOR PLANTING							
			1		0.01		0.000,1		10^{-6}	
			Dry	Natural	Dry	Natural	Dry	Natural	Dry	Natural
Human Avirulent	Control		3*	2	2	3	3	3	5	5
	6 months	Incubator (37°C.)	0	4	0	0	0	0	0	0
		Room (20°–25°C.)	3	3	3	4	6^{1}	5	6^{2}	0
		Refrigerator (3°C.)	2	3	3	3	3	4	4^{1}	4^{1}
	1 year	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	4	0	0	0	0	0
		Refrigerator	4	4	3	4	3	4	6^{1}	5^{1}
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	4	0	4	0	4	0	0	0
	3 years	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	2	0	3	0	4	0	4^{1}	0
Virulent Human H7	Control		2	2	3	3	4	3	4^{1}	5
	6 months	Incubator	0	5^{1}	0	0	4^{1}	0	0	0
		Room	3	5	4	0	0	0	0	0
		Refrigerator	3	2	3	3	3	3	0	5^{2}
	1 year	Incubator	0	0	0	0	0	0	0	0
		Room	5	0	0	0	0	0	0	0
		Refrigerator	3	4	3	3	4	4	0	0
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	2	0	2	0	3	0	0	0
	3 years	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	3	0	3	0	4^{1}	0	0	0

* The numeral indicates the number of weeks after which the first growth was noted.

The exponent indicates the number of tubes of three that became positive when all were not positive.

0 indicates that no growth occurred.

conditions were viable. The virulent avian strain (Avian 3) showed a fairly good survival (see table 2) up to two years for the nondesiccated

TABLE 2

Effect of storage upon the viability of natural and desiccated tubercle bacilli

STRAIN OF BACILLI	TIME INTERVAL	STORAGE TEMPERATURE	AMOUNT OF SUSPENSION IN MG. PER CC. USED FOR PLANTING							
			1		0.01		0.000,1		10^{-4}	
			Dry	Natural	Dry	Natural	Dry	Natural	Dry	Natural
Virulent Bovine, Bov. Vir.	Control		2*	2	3	3	3	4	4	5
	6 months	Incubator (37°C.)	2	0	3	0	3	0	0	0
		Room (20°–25°C.)	2	0	3	0	3	0	3	0
		Refrigerator (3°C.)	2	3	2	4[2]	3	0	0	0
	1 year	Incubator	4	0	5	0	8	0	6[2]	0
		Room	2	0	3	0	5	0	8	0
		Refrigerator	2	0	2	0	4	0	8	0
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	3	0	0	0	0	0	0	0
		Refrigerator	2	0	2	0	3	0	0	0
	3 years	Incubator	0	0	0	0	0	0	0	0
		Room	3	0	4	0	5[1]	0	0	0
		Refrigerator	2	0	2	0	3	0	3	0
VirulentAvian, Av. 3	Control		3	2	3	3	5	3	5	4
	6 months	Incubator	3	0	4	0	4	0	0	0
		Room	2	0	2	0	3	0	4	0
		Refrigerator	2	0†	2	0	3	0	4	0
	1 year	Incubator	6[1]	0	7[1]	0	0	0	0	0
		Room	3	0	4	0	6	0	0	0
		Refrigerator	3	3	3	3	4[1]	4	6	4
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	4	0	0	0	0	0	0	0
		Refrigerator	2	5	3	5[2]	3	0	6	0
	3 years	Incubator	0	0	0	0	0	0	0	0
		Room	4	0	4	0	0	0	0	0
		Refrigerator	2	0	3	0	4	0	0	0

* The numeral indicates the number of weeks after which the first growth was noted; 0 indicates that no growth occurred.

† For unaccountable reason, this sample appeared not to be viable at this interval but was later.

tests, up to two years (in the 0.01 mg. dilution) at refrigerator temperature, while at incubator and room temperatures loss of viability was

complete after six months. The desiccated bacilli, on the other hand, survived fairly well for three years (to the 0.000,1 mg. dilution) at refrigerator temperature.

TABLE 3

Effect of oxygen and nitrogen upon the viability of natural and desiccated virulent human tubercle bacilli (H7) maintained at different temperatures

GAS USED	TIME INTERVAL	STORAGE TEMPERATURE	AMOUNT OF SUSPENSION IN MG. PER CC. USED FOR PLANTING							
			1		0.01		0.000,1		10^{-6}	
			Dry	Natural	Dry	Natural	Dry	Natural	Dry	Natural
Oxygen	Control		2*	1	2	1	3	2	4	2
	6 months	Incubator (37°C.)	0	0	0	0	0	0	0	0
		Room (20°–25°C.)	3	0	0	0	0	0	0	0
		Refrigerator (3°C.)	2	2	3	3	9^1	3	0	3
	1 year	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	3	3	3	3	0	3	0	3
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	3	2	3	3	0	4	0	0
Nitrogen	6 months	Incubator	3	0	3	0	5	0	0	0
		Room	3	0	3	0	3	0	4^2	0
		Refrigerator	3	2	3	3	3	3	4	3
	1 year	Incubator	3	0	0	0	0	0	0	0
		Room	3	0	3	0	5^1	0	0	0
		Refrigerator	3	3	3	3	8	4	0	4
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	5	0	5	0	0	0	0	0
		Refrigerator	2	2	3	2	4	3	0	3

* The numeral indicates the number of weeks after which the first growth was noted; 0 indicates that no growth occurred.

The exponent indicates the number of tubes of three that became positive when all were not positive.

The rapid loss of viability of the nondesiccated specimens in all cases as compared with the desiccated specimens of human, bovine and avian tubercle bacilli made it necessary to determine the effect of the presence of oxygen or moisture as factors in hastening the destruction of the viability of the bacilli. To test this, human tubercle bacilli (virulent,

H7 (see table 3) and avirulent (see table 4)) sealed in oxygen or nitrogen were studied, using both desiccated and natural specimens.

TABLE 4

Effect of oxygen and nitrogen upon the viability of natural and desiccated avirulent human tubercle bacilli maintained at different temperatures

GAS USED	TIME INTERVAL	STORAGE TEMPERATURE	AMOUNT OF SUSPENSION IN MG. PER CC. USED FOR PLANTING							
			1		0.01		0.000,1		10^{-6}	
			Dry	Natural	Dry	Natural	Dry	Natural	Dry	Natural
Oxygen	Control		2*	2	2	2	2	2	4	3
	6 months	Incubator (37°C.)	0	0	0	0	0	0	0	0
		Room (20°–25°C.)	0	0	0	0	0	0	0	0
		Refrigerator (3°C.)	3	5	0	0	9^{1}	0	0	0
	1 year	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	3	0	3	0	4	0	0	0
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	0	0	0	0	0	0	0	0
		Refrigerator	4^{1}	0	0	0	3^{1}	0	0	0
Nitrogen	6 months	Incubator	0	0	0	0	0	0	0	0
		Room	3	0	3	0	3	0	3	0
		Refrigerator	3	3	3	3	3	3	0	3
	1 year	Incubator	4	0	0	0	0	0	0	0
		Room	3	0	3	0	4	0	0	0
		Refrigerator	3	3	3	3	3	4	5	4
	2 years	Incubator	0	0	0	0	0	0	0	0
		Room	5	0	5^{1}	0	4^{2}	0	0	0
		Refrigerator	4	0	3	0	3	0	3	0

* The numeral indicates the number of weeks after which the first growth was noted; 0 indicates that no growth occurred.

The exponent indicates the number of tubes of three that became positive when all were not positive.

The results recorded in tables 3 and 4 show that the presence of oxygen markedly accelerates the loss of viability of both the virulent and avirulent human tubercle bacilli whether in dry or natural state. After six months of incubator and room temperature, the bacilli sealed with

oxygen were practically killed in all dilutions (the incubator temperature proved more destructive to viability than the room temperature in all cases), while those sealed with the nitrogen were alive at incubator temperature up to one year in heavy plants (1 mg.) and at room temperature up to two years in 0.01 mg. dilutions. At refrigerator temperature, survival was good in both the desiccated and natural specimens whether in oxygen or nitrogen (although slightly better in nitrogen) in high dilution of the bacilli (0.000,1 and 0.000,001 mg.).

The obvious conclusions are that the destruction of human tubercle bacilli, regardless whether desiccated or natural, is primarily a function of temperature and that the rate of destruction is greater in the presence of oxygen than in air or nitrogen, respectively. Desiccation, although a minor factor, aids in maintaining the viability of tubercle bacilli.

The macroscopical appearance of the moist (natural) culture in the sealed tube varies with the temperature and the age of storage. Decomposition and pigmentation occur as early as six months at incubator temperature, slightly at room temperature, and not at all at refrigerator temperature. With the desiccated bacilli, only slight changes are perceptible.

The strikingly fascinating feature of all these investigations is the fact that a high percentage (70 or more) of the water and volatile material can be removed from the bacilli without a perceptible deterimental effect upon viability. Rapid desiccation is apparently more protective than slow desiccation, although the obvious explanation might be the effect of extraneous toxic materials accumulating in one case and not the other. Potter's work as well as ours makes it highly desirable that an explanation be sought for the resistance of tubercle bacilli to extreme desiccation, to extremes of cold (liquid air), as well as high vacua. We have found no effect upon the virulence of the bacilli by these drastic procedures.

SUMMARY

Desiccated human (virulent and avirulent), bovine (virulent), and avian (virulent) tubercle bacilli almost completely retain viability for three years at refrigerator temperature, while natural cultures survive under the same condition of temperature only about six months to one year (occasionally two years). The loss of viability of the desiccated cultures of these same strains of tubercle bacilli is much more rapid at incubator temperature, being almost complete at six months to one year;

while at room temperature, they survive a little better than at incubator temperature.

The loss of viability of tubercle bacilli is primarily a function of the temperature at which they are stored, regardless whether they are desiccated or natural. The rate of loss of viability of cultures of tubercle bacilli is greater in the presence of oxygen, less so in the presence of air and least in nitrogen. Desiccation, although a minor factor, aids in maintaining the viability of tubercle bacilli. Desiccation can remove as much as 70 to 75 per cent of the water (and volatile materials) from the cultures of tubercle bacilli without appreciable detrimental effect on the viability. Aside from the preservation of well grown broth cultures of mammalian tubercle bacilli (some of the bacilli remaining viable for over twelve years, as described by us in 1933 (2)), cultures of strains of mammalian and avian tubercle bacilli can be preserved in viable form for over three years when desiccated and sealed in air or nitrogen and maintained at refrigerator temperature. The latter method possesses advantages over the former in that the specimens occupy little space and are readily transportable.

I wish to thank Mr. L. D. Miller for assisting with the technical phases of this study.

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TUBERCLE BACILLI SUSPENDED IN GASTRIC MUCIN[1, 2]

Their Pathogenicity for Guinea Pigs

MOORE A. MILLS AND CHARLOTTE A. COLWELL

In studying experimental pulmonary tuberculosis in dogs it was found desirable to incorporate the suspensions of tubercle bacilli in some cohesive material which would tend to localize the inoculation in one site and so prevent or limit early bronchial dissemination or expulsion of the inoculum by coughing, and which would at the same time have little more than a possible mechanical effect upon the genesis or progress of the lesion. As sterilized gastric mucin has been shown to produce only slight local reactions when injected alone into the pulmonary parenchyma (1) and in other respects appeared to be an ideal material, it was considered necessary, in view of the reported alterations in pathogenicity which occur when pneumococci and other organisms are incorporated in this material before injection (2), to determine if any similar enhancement of virulence could be demonstrated for the tubercle bacilli.

Nungester, Wolf and Jourdonais (3) first observed that pneumococci suspended in gastric mucin and injected intraperitoneally were apparently more virulent than were suspensions of the same cultures in saline. This apparent enhancement of virulence was demonstrated also for various strains of streptococci, staphylococci, *E. coli*, *M. catarrhalis* and *B. subtilis* (3, 4). Miller (5) later showed that similar alterations in pathogenicity occurred when meningococci were suspended in mucin before injection. Although the exact mechanism by which mucin produces this alteration of pathogenicity or apparent enhancement of virulence has not been clearly defined it is probable that the viscous material acts more or less mechanically by protecting the bacteria from the body cells and fluids during the early stages of their residence in the host, thus permitting early multiplication and establishment of the inflammatory lesion (4). The experience of Robertson and his co-

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[2] Aided by a grant from the Committee on Scientific Research of the American Medical Association.

workers (6, 7) with suspensions of pneumococci in viscous sterile solutions suggests that the viscosity of the medium is the significant factor rather than any specific chemical action of the mucin. If this is the case, then mucin can be presumed to exert an effect only so long as its viscosity is maintained in the presence of tissue fluids, perhaps for only a period of hours. One would expect, therefore, that it would have no more than a slight influence upon the establishment of a tuberculous lesion and perhaps no effect whatsoever upon the final outcome of the disease. As no reports have appeared in the literature which have a bearing on this problem, we have undertaken the following study, a comparison of the local primary lesions and generalized tuberculosis produced by mucinous suspensions of tubercle bacilli injected subcutaneously with that produced by saline suspensions of the same culture.

METHODS

Suspensions of gastric mucin were prepared by adding 20 g. of commercial gastric mucin (Armour) to 100 cc. of distilled water and autoclaving in wide-mouthed bottles for fifteen minutes at twenty pounds pressure. A flocculent precipitate forms which settles on standing and the clear supernatant solution is withdrawn for use. This method of preparation is now commonly used and yields a product which has an adequate viscosity and represents a 5 to 10 per cent solution.

Human type tubercle bacilli, strain "G II," were employed in the experiments. This strain, isolated in 1930 from a fatal case of tuberculous meningitis, is of known high virulence for guinea pigs. Suspensions were prepared from three to four weeks old cultures grown on glycerin-egg-yolk medium. Three to four large loopfuls of growth were ground with sterile ox-bile in an agate mortar to facilitate dispersion and about 5 cc. of sterile saline added slowly with further grinding. The heavy suspension thus prepared was allowed to stand for thirty minutes for the larger clumps to settle before computing the bacillary content by centrifugating 1 cc. in a Hopkin's tube (vaccine) at high speed for thirty minutes. The suspensions for injection were prepared by diluting a quantity of the measured heavy suspension with saline, so that in the final dilution 1 cc. of the saline suspension added to 9 cc. of sterile mucin contained the desired doses of tubercle bacilli. Control suspensions were diluted to the same volume with 0.9 per cent saline. All suspensions employed in these and other experiments have been prepared by this method and it is felt that the relative accuracy of the measurements of such bacillary suspensions may be relied upon.

Sixty guinea pigs weighing 300 to 400 g. were divided into six groups which received respectively 0.25 mg., 0.05 mg., 0.005 mg., 0.000,5 mg., 0.000,05 mg. and 0.000,005 mg. of tubercle bacilli. One-half cc. amounts of the suspensions were injected subcutaneously in the left groin, one-half of the animals in each group being injected with mucinous suspensions, the other half with saline suspensions to serve as controls. The animals were maintained on the standard laboratory diet and were weighed at weekly intervals. The appearance and relative sizes of the local nodules thus produced, as well as the appearance of ulcera-

TABLE 1

GROUP NUMBER	SUSPENSION	AVERAGE WEIGHT CHANGE	AVERAGE SIZE OF NODULES (CM.) AT NECROPSY	PER CENT ULCERATION	AVERAGE AMOUNT TUBERCULOSIS AT NECROPSY
I (0.25 mg.)	Mucin	−55 g.	1.5—0.85—0.25	0	++++*
	Saline	−73 g.	1.0—0.45—0.25	0	++++*
II (0.05 mg.)	Mucin	−64 g.	1.0—0.50—0.50	0	++++*
	Saline	−65 g.	1.0—0.70—0.50	0	++++*
III (0.005 mg.)	Mucin	−114 g.	1.8—1.20—1.20	0	++++*
	Saline	−108 g.	1.8—1.60—1.00	0	++++*
IV (0.000,5 mg.)	Mucin	−84 g.	2.2—1.30—0.90	20	++++*
	Saline	−47 g.	1.7—1.10—0.90	0	++++*
V (0.000,05 mg.)	Mucin	+106 g.	4.5—1.50—1.00	85	++++
	Saline	+69 g.	2.9—1.20—0.90	50	+++
VI (0.000,005 mg.)	Mucin	+86 g.	4.3—1.25—0.90	85	++
	Saline	+53 g.	2.8—0.90—0.60	0	+++

* Died of tuberculosis.

tion and evacuation of contents, were noted. Animals dying at any time during the course of the experiments were autopsied and a control animal from the same group was picked at random and sacrificed at the same time. Four animals with suitable controls were picked at random from the two groups injected with the smallest doses and sacrificed after 76 days. The experiment was terminated by sacrificing the remaining animals after 110 to 112 days.

RESULTS

The significant results are contained in table 1. The data for each group have been averaged with a view to conserving space, as the differ-

ences noted between the disease in the animals receiving mucinous suspensions as compared with the controls were so slight that further tabulation appeared to be unwarranted. The extent of the tuberculosis found at autopsy was arbitrarily graded from one to four plus in terms of the size and number of lesions occurring locally, in lymph nodes, spleen, liver and lungs. These figures were averaged and have been included in the table as one figure representing the extent of the tuberculosis in each group.

As can be seen in table 1, no significant differences appear in groups I to III with respect to the size of the local nodule, tendency to ulceration, weight changes or extent of the disease at autopsy. The guinea pigs of group I died of tuberculosis between 15 and 24 days, the deaths occurring with equal frequency in the mucin and control animals. This was also true in group II, the deaths occurring between 17 and 27 days, and in group III the animals of which died of tuberculosis in periods between 39 and 51 days. The first three groups received 0.25 mg., 0.05 mg. and 0.005 mg. of tubercle bacilli, respectively.

In the groups receiving the smaller doses, namely, 0.000,5 mg., 0.000,05 mg. and 0.000,005 mg. of tubercle bacilli, somewhat more marked and more constant differences were noted. The animals of group IV died of tuberculosis between 49 and 80 days after injection. The animals of the remaining two groups were sacrificed at 76 days and 110 to 112 days, with the exception of two control animals in group V which died at 97 days and 110 days respectively. Although the weight changes and, more important, the extent of the tuberculosis found at autopsy were without significant difference, the extent of the local lesions in the groins of the animals injected with the mucinous suspensions, and the tendency of these lesions to ulcerate and discharge their contents were significantly greater than in the animals injected with saline suspensions. The average size of the lesions in the guinea pigs of the mucin series was approximately twice that of the saline controls. In the same groups, 69 per cent of the lesions in the mucin series ulcerated and discharged, as compared with 19 per cent of the controls.

SUMMARY AND CONCLUSIONS

Sixty guinea pigs were injected subcutaneously with varying doses of tubercle bacilli, equal numbers receiving bacilli suspended in mucin and in saline, for the purpose of determining whether or not any alteration of pathogenicity would occur with the organisms suspended in

mucin. No significant differences could be noted with the exception that, of the guinea pigs receiving the smallest doses, those injected with mucinous suspensions developed larger local lesions which showed a greater tendency to ulcerate and discharge their contents. This effect may be explained upon a purely local and mechanical basis. The injected mucin, because of its viscosity, may act temporarily in maintaining a high concentration of bacilli at the site of injection, promoting the development of a more extensive local lesion. With the gradual disappearance of the mucin, the infection progresses in a manner similar to that seen in guinea pigs injected with saline suspensions.

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BOOKS

JAMES ALEXANDER MILLER AND ARVID WALLGREN: *Pulmonary Tuberculosis in Adults and Children. Pp. 193, with 73 illustrations, Thomas Nelson & Sons, New York, 1939, fabrikoid, $3.50.*

By ELI H. RUBIN

From a number of renewal sections in the latest revision of Nelson's New Loose-Leaf Medicine, two articles on tuberculosis are reprinted in book form. Doctor Miller's contribution deals with pulmonary tuberculosis in adults; Doctor Wallgren's with tuberculosis in children. In estimating the value of the book due consideration must be given to the fact that the volume consists primarily of renewal pages in a system of medicine, many aspects of the subject having been treated by other contributors. The part dealing with tuberculosis in adults precedes that devoted to tuberculosis in children; the reverse arrangement might have been more desirable since the latter gives a better insight into the initial phases of the disease. It would also have prevented a certain amount of duplication.

Doctor Miller's description of the evolution of pulmonary tuberculosis is based essentially on the researches of the German school in which Ranke's teachings occupy a prominent place. The classification of pulmonary tuberculosis follows more rigidly a pathogenic pattern than has been attempted by others in English textbooks. Its practical value in every-day practice is open to question. Tuberculosis is described under the following three basic forms:

I. *Nonphthisical Forms*
   1. Primary
   2. Acute miliary
   3. Protracted multiform
   4. Chronic disseminated

II. *Prephthisical Forms*
   1. Clinically manifest early acute phase: (a) Discrete, miliary-like dissemination; (b) Pleural effusions, (c) Reticular lymphangitis
   2. Latent, only roentgenologically manifest phase: (a) Diffuse fibrosis, (b) Nodular fibrotic or calcareous apical and subapical foci

III. *Phthisical Forms*
   1. Early phthisis: (a) Insidious incipient phthisis (with fibroulcerative lesions), (b) Early acute infiltrative phthisis (with fresh and moderate cavitation)
   2. Established phthisis: (a) Diffuse cirrhotic cavitary phthisis, (b) Relapsing fibrocaseous cavitary phthisis
   3. Terminal (broncho- or lobar) pneumonic phthisis

The clinical aspects are presented briefly. Considerable emphasis is placed on blood changes, symptoms receive passing notice, by comparison. Since the book is addressed to medical students and general practitioners, the symptomatology might have been enlarged upon to advantage. The importance of the finding of tubercle bacilli in the sputum is stressed; possibly too little importance in differential diagnosis is given to the evaluation of negative sputum. Significant of the recent orientation in the diagnosis of pulmonary tuberculosis is the placing of the roentgen examination under the heading devoted to physical examination.

The clinical course of the disease is considered in the light of its pathogenetic background, as outlined previously. The clinico-roentgenological description places major emphasis on X-ray examination. The reader is referred to illustrative case reports for more details concerning the history and symptoms. Much of the discussion is concerned with generalized and prephthisical stages of tuberculosis. The common garden varieties of the disease, as they come to the practitioner's attention, are covered too briefly.

The chapter dealing with treatment follows the standard pattern. More space is devoted to a consideration of the time of reëxpansion of pneumothorax, a problem that usually solves itself, than to the indications for induction. The pathogenesis of the disease is well illustrated, but not a single illustration is included to show how treatment by pneumothorax, diaphragmatic paralysis or thoracoplasty registers on the X-ray film.

The advanced student in tuberculosis will find much in this part of the book stimulating; the beginner and general practitioner who still have to depend on the history, physical examination and the X-ray findings will not find the treatise adequate to meet his needs.

The second part of the book, by Doctor Wallgren, is a finished product. In clear and concise statements, frequently italicized, the modes of infection, the portals of entry and the course of tuberculosis in children are described. Attention is directed to the decreasing incidence of the disease in recent years and to the paradox of different death rates at various ages in the presence of a steadily increasing infection rate from infancy to advanced age. Particularly detailed is the description of the period of incubation, a subject to which the author has contributed many original studies. It is emphasized that, aside from tuberculin sensitivity, the primary tuberculous infection behaves clinically in the same manner as an acute infectious disease. During this stage there is haematogenous spread of tubercle bacilli resulting in infection of various organs of the body.

In the majority of infected persons the tuberculous process becomes arrested following the primary infection. In a small number, postprimary tuberculosis occurs. The latter is divided into two forms: (*1*) secondary tuberculous diseases which appear shortly after the primary infection and which take the

forms of miliary tuberculosis, tuberculous meningitis, serous pleurisy and peritonitis, disseminated tuberculosis of the skin, certain lung infiltrations and (*2*) tertiary tuberculous diseases which develop in children who have passed through the primary or the secondary tuberculous diseases. Representatives of this group are phthisis, tuberculosis of bones and joints, genitourinary tuberculosis and lupus. Later chapters amplify this classification.

On the question of the relation of allergy to immunity the author takes a middle-of-the-road stand. Infection which induces tuberculin sensitivity also produces a manifest increase of resistance to new exogenous infection, that is, it induces a relative immunity. To the individual, however, the most important factor is the natural resistance and the final result of the tuberculous infection rests solely on that. Allergy must be regarded as something undesirable, inasmuch as it determines the intensity of the necrotic reaction in disease processes. On the other hand, the specific immunity following a tuberculous infection must be regarded as a favorable property.

Since the most valuable aid in diagnosing tuberculosis in children is the tuberculin test, the author devotes a complete chapter to this phase of the problem. He details the pitfalls of nonspecific reactions, the significance of positive and negative reactions, conditions which decrease tuberculin allergy and the several methods of performing a tuberculin test.

The main body of the monograph is devoted to an enlargement of the three-stage classification referred to previously. Noteworthy is the wealth of clinical material utilized: symptomatology, clinical signs, and laboratory aids, interpreted in the light of pathological changes. Considerable prominence is given to *erythema nodosum* fever as the initial fever of tuberculous infection.

The chapter on prognosis deals with the immediate outlook of tuberculosis on children and with the final issue of the tuberculous infection. Early prognosis and late prognosis depend on widely different factors and are in no way related to each other. The author ascribes considerable importance to the fever curve and the rate of the sedimentation reaction, determined periodically. He does not consider the demonstration of tubercle bacilli in the gastric contents of prognostic significance inasmuch as bacilli are found in the majority of tuberculous infants.

The principles underlying treatment and prevention of tuberculosis in children are discussed lucidly. The author does not subscribe to pneumothorax treatment of the primary infection. The indications for this treatment in ulcerative tuberculosis are not discussed.

Doctor Wallgren's monograph on tuberculosis in children is among the most enlightening descriptions that have appeared on the subject in the English language. Within the confines of less than two hundred pages, Doctor Miller and Doctor Wallgren give a wealth of information much of which is not available in standard textbooks. The arrangement of headings and subheadings and the double columns contribute to the readability of the volume.

GEORGE W. NORRIS AND H. R. M. LANDIS: *Diseases of the Chest and the Principles of Physical Diagnosis. Sixth edition, revised. Contributors: Simon S. Leopold, Charles M. Montgomery and Thomas M. McMillan. Pp. 1019, with 478 illustrations, Philadelphia and London, W. B. Saunders Company, 1938, cloth, $10.00.*

By JOHN B. SCHWEDEL AND MAX PINNER

The portions of the new sixth edition of this book devoted to diseases of the heart have been extensively altered and amplified. Dr. Thomas M. McMillan has written an entire new section on electrocardiography which for sheer lucidity and condensation marks it as one of the highlights of the book, sufficiently simple to be easily understood by the student and medical practitioner. It is, therefore, more the pity that an edition published in August, 1938 still employs the old IVth or precordial leads, whereas the new criteria now generally accepted have been available since early in the same year.

The section on X-ray of the heart and great vessels is a welcome addition to the book and should be of considerable diagnostic value. The fluoroscope today should be considered as much a part of the examination as auscultation, and certainly far more valuable than percussion. By fluoroscopic methods cardiac enlargement can readily be determined, not only as a whole, but also in its constituent parts. Individual chamber enlargement is of particular value in arriving at an exact diagnosis. More attention to criteria for chamber enlargement and less emphasis on cardiac measurement would seem desirable.

Additional methods of examination, such as circulation time, vital capacity and basal metabolism, have also been added and are as welcome as the omission of polygraphs and sphygmographs which are more or less dated.

The chapters devoted to diseases of the pericardium, myocardium and endocardium have undergone considerable revision and addition. The mechanisms involved in congestive failure, gallop rhythm and heart sounds are very much up-to-date. Many other sections including that on angina pectoris have been completely rewritten. Exception must be taken to the classifications of heart disease by aetiology other than those accepted by the American Heart Association and in general use in most of the country.

The impression of the portions dealing with diseases of the heart, is extremely favorable, and they are as valuable to the internist as to the medical student who probably will use them most.

The chapters dealing with the diagnosis of respiratory diseases will continue to be very useful both to students and practitioners. The physical signs are completely enumerated and explained, but their diagnostic significance and limitations are not sufficiently discussed; this deficiency is felt all the more because they are presented in a chapter divorced from their clinical use. The proper evaluation of physical signs probably cannot be taught in a living and impressive manner without direct application to clinical problems.

With succeeding editions of a successful textbook, it eventually becomes necessary to rewrite instead of revise. This necessity is much felt in the chapter on pulmonary tuberculosis. The epidemiological data are quite antiquated. The description of the initial changes in pulmonary tuberculosis as "apical catarrh" hardly belongs in a modern textbook. That cavities are due in large part to the action of "the various pus-producing organisms" is definitely not "the present belief." The inclusion of ulcerative and stenotic disease of the large bronchi is sorely needed. There is no discussion of the early asymptomatic infiltrative lesions, a particularly unfortunate omission in a textbook whose main emphasis is on diagnosis. The rôle of roentgenology in the diagnosis is not stressed, but is presented in separate paragraphs occupying less than two pages, and there is a total of two roentgenograms presented in the section on pulmonary tuberculosis, while otherwise the illustrations are profuse. The curious underestimation of the rôle of roentgen studies in tuberculosis is well exemplified by the following (italicized) sentence: "The recognition of true incipient tuberculosis cannot be accomplished except by careful consideration of the facts revealed in the history and a proper estimation of the slight deviation from normal as revealed by inspection, palpation, mensuration and percussion." No mention of the sovereign rôle of roentgenology is made in this connection. It can be confidently expected that Doctor Leopold, who has undertaken the further revision of the respiratory chapters, will completely modernize this chapter on tuberculosis in future editions.

The chapters dealing with other bronchial and pulmonary diseases, particularly those on bronchiectasis, abscess, cystic disease and atelectasis, deserve high praise. Here, solid and up-to-date information is presented in clear and concise writing, and these chapters are warmly recommended not only to the student but to the specialist and general practitioner as well.

HAQVIN MALMROS AND ERIK HEDVALL: *Studien über die Entstehung und Entwicklung der Lungentuberkulose. Pp. 223, with 140 illustrations, 1938, Johann Ambrosius Barth, Leipzig, paper.*

By MAX PINNER

That the opinions about the initial phases of pulmonary tuberculosis have undergone considerable changes and are far from being settled and unanimous is clearly shown in the introductory chapter of this book, in which these developments are discussed with lucid and concise objectivity. This historical chapter makes obvious the need for just such studies as are presented—and for many more. Since the authors had in Lund a material with a relatively low incidence of tuberculin reactors, they had over the period of nine years, covered by their observations, a considerable number of persons whom they

could study from the anergic to the allergic phase. This study comprises more than 3,000 students and student nurses. There were 151 persons who became tuberculin-positive; 104 did not show any signs or symptoms while becoming positive. In 47, tuberculous changes were demonstrated which consisted of the traditional primary complex in only 21 of the 47. It is significant that in 14 cases pulmonary tuberculosis developed following the primary infection without the interpolation of a demonstrable primary complex or hilar adenitis; this occurred in most cases without symptoms. The first parenchymal shadows indicative of pulmonary tuberculosis, as contrasted with the primary complex, consist of small scattered cloudy spots, and not of single infiltrates. These foci that were regularly observed as the first lesions of progressive pulmonary tuberculosis are termed "subprimary initial foci."

In a second group of 43 patients are included all those who were tuberculin-positive at first examination, but who had no demonstrable tuberculous foci, but developed such under observation (37 pulmonary tuberculosis, 2 hilar adenitis, 4 pleuritis). Of the 37 cases of pulmonary tuberculosis, 28 showed the characteristics of the above described initial foci, the remainder showed infiltrates. In these cases there was considerable tendency to serious progression and excavation in contrast to the frequent absence of symptoms and to the usually normal sedimentation rate.

It is impossible to mention all the details of this study which, in this reviewer's opinion, is a most significant contribution to the pathogenesis of tuberculosis. It needs to be emphasized that the majority of primary lesions are accompanied by symptoms, while most "initial foci" develop asymptomatically. The pertinent time relations between allergization, primary manifestations and pulmonary tuberculosis deserve the most attentive study.

A total of 136 summarized case reports, illustrated by 136 roentgenograms, are presented. The illustrations deserve special mention. The cuts were made by the Graphic Institute in Malmö, Sweden. Wisely sacrificing the showy quality of contrast, the Institute has produced reproductions that are probably unsurpassed in detail. It is rare indeed to see roentgenographic reproductions that are such faithful pictures of the original films.

For sheer richness of the material studied and for completeness of the observation, this work is probably unique. How far the deductions are generally acceptable must be decided by other series of observations that should be not less complete. Such future work from different countries must show especially which, if any, features in these observations are particular to the country or to the human stock on which they are based.

In the meantime, Doctor Malmros's and Doctor Hedvall's work will stand as a most important development in our knowledge of the early phases of tuberculosis. It is warmly recommended for careful study to all interested in the theoretical aspects of pathogenesis and in the diagnosis of genuinely early tuberculosis.

S. A. WEISMAN: *Your Chest Should Be Flat. Pp. xvii + 145, with 74 illustrations and 17 tables, J. B. Lippincott Company, Philadelphia, 1938, cloth, $2.00.*

By LEWIS J. MOORMAN

In this small volume of 145 pages, with many tables and illustrations, the author presents an impressive array of observations based upon an exhaustive effort to correct the long-standing belief, on the part of many, that the flat chest predisposes to tuberculosis. He very properly points out that this error is due to the fact that, upon superficial inspection, the round deep chest appears to be flat and "sunken in." The author's careful investigations, extending over a period of twelve years, include measurements of approximately 20,000 school children, supplemented by similar measurements of many patients suffering from pulmonary tuberculosis. His statistical findings afford conclusive evidence that the round deep chest is associated with a definite predisposition to manifest pulmonary tuberculosis, whereas the flat chest offers greater resistance to the disease. In the past, a few exceptionally keen observers have noted this predisposition. As early as the latter part of the eighteenth century, Portal, in a discussion of pulmonary haemorrhage in young people, considered the small narrow chest as a causative factor. Others have made similar observations and, as shown by the author, during the past few decades certain studies in thoracic mensuration have suggested the relationship between the round deep chest and manifest pulmonary tuberculosis, which is so well authenticated in this interesting little book with its arresting title.

The second chapter, dealing with the normal development of the chest, shows that the round deep infantile type is normally so rapidly transformed that by the end of the fifth year the configuration of the chest closely approximates the flat chest of the normal adult. Though the transformation slowly proceeds until the eighteenth year is reached, it is important to remember that the opportunities for normal development of the chest are largely limited to the first five years of life. This is doubly important when we consider that in the fifth chapter it is claimed that environment is the determining factor in the development of the chest and that stock or heredity has little influence.

If environment determines the type of chest, and if its influence is exerted chiefly within the first five years of life, it is imperative that those who determine the environment during this period of the child's life should have the information contained in Doctor Weisman's book.

The eighth chapter is devoted to a discussion of defences. Methods of building a well developed normally shaped chest are well presented. Fortunately the author stresses the fact that building a normal chest is to be

considered as only one of many preventive measures now employed against the development of tuberculosis.

It is unfortunate that, throughout the book, the terms "tuberculous chest" and "tubercular chest" are employed as being synonomous with the round deep chest, which should be considered only as a predisposing condition.

Naturally certain interrogations arise. Is the round deep chest the chief factor in the development of manifest tuberculosis, or is the disease a result of the same environment which causes the chest to be round and deep? Is the round deep chest more susceptible to infection than the flat chest, or is the character of the soil in the abnormally developed chest responsible for the increased incidence of manifest disease in such cases?

Your Chest Should be Flat is heartily recommended to everyone interested in tuberculosis, and particularly to all who are concerned with the development of the child.

JACQUES STÉPHANI: *Études radiographiques du poumon tuberculeux. Pp. 140, with 205 figures, Paris, Amédée Legrand, Éditeur, 1939, paper, 45 fr.*

By FRIEDRICH G. KAUTZ

This volume presents a method of interpreting pulmonary lesions by means of shaded tracings from roentgen films. For several years the author has systematically applied this method and has contributed several studies on it. This book is a collection of previous publications on the subject which have been brought up to date by additional material. It gives a comprehensive account of interpretation of normal pulmonary markings and of tuberculous lesions. In thirteen chapters with numerous illustrations of the authors drawings, the border-line between normal and pathological appearance is particularly stressed and at the end of each chapter is a summary of the clinical, prognostic and therapeutic advantage of the method. Pulmonary cavities lend themselves particularly well as a subject for this method and the results of large series of consecutive observations of the different types and their development are set forth in several chapters. The characteristics of the early infiltrate and of cavities, of their natural course and of the closure of cavities under conservative and under collapse therapy are clearly described in the text and illustrations. By means of tracing cavities the reader of roentgen films can more easily distinguish between the well delineated and the faintly visualized cavity. The author feels that the latter type of cavitation which is ill defined and barely seen on the film, having neither a well delineated wall of annular atelectasis nor an appreciable amount of fluid, shows a rather unfavorable course and therefore should be treated with collapse therapy at an early

stage. Thus, carefully interpreted radiological findings may explain why certain types of cavities fail to show any natural tendency to close. Other chapters are devoted to contralateral cavities in cases of an artificial pneumothorax, to the primitive cavity of the "mongolfiere-type," to the giant cavity, to the formation of cavities in areas of previously scarred or apparently fibrosed lesions, and to the occurrence of cavities in the partially collapsed lung. The conclusions are interesting, stimulating and helpful in bringing the problems that arise from the manifold pathophysiological development of cavities to a closer interpretation and to a better understanding. The author is well aware of the fact that his method is subject to the variation of individual judgment and interpretation and, therefore, wisely refrains from pushing the results and conclusions from the roentgenological findings beyond reasonable limits. He merely emphasizes the importance of tracing pulmonary lesions for the purpose of demonstration and of teaching. Thus, his method constitutes a valuable aid for the correlation of the roentgenological interpretation with the assumed pathological lesions.

WILLIAM H. FELDMAN: *Avian Tuberculosis Infections. Pp. ix + 483, with 109 figures, Baltimore, The Williams & Wilkins Company, 1938, cloth, $7.00.*

By MAX PINNER

Since the great economic significance of the avian tubercle bacillus has been recognized as disease producer both in fowl and swine, the literature has grown to considerable magnitude, and interest in this microörganism has been revived. A critical and complete analysis is, therefore, most welcome; this Doctor Feldman presents in a highly satisfactory form. The material on hand, supplemented by significant contributions by the author, seems to be complete; it is arranged in lucid and logical sequence; it is critically digested and concisely summarized; it is documented by an appalling wealth of data; it is illustrated with many well chosen figures whose high quality of perfection (including the typographical reproduction) sets a high standard; the bibliographical references are abundant; the style is pleasant and readable.

As to the contents, it should be pointed out that this book contains many observations of great interest beyond the specific field of avian tuberculosis. A complete concept of mycobacterial diseases requires knowledge of the fundamental tissue responses caused by mycobacteria of different degrees of pathogenicity in animals of different degrees of susceptibility. In other words, Doctor Feldman's book adds an important chapter of comparative pathology (and immunology) to the story of tuberculosis. This chapter deserves careful study by all workers in tuberculosis.

Of particular interest to the clinical man is the extensive chapter on avian tuberculosis in man. In this chapter, Doctor Feldman's critical labor is highly praiseworthy. By careful analysis it is shown that, of the many casuistic reports of avian infection in man, only thirteen can be accepted as satisfactorily proved cases, indicating "that human beings have a formidable resistance to this particular form of the tubercle bacillus. The opportunities for infection are numerous. . ."

The publisher should be congratulated upon a particularly pleasing and beautiful job of book-making.

JOHN H. NORTHROP: *Crystalline Enzymes, The Chemistry of Pepsin, Trypsin and Bacteriophage. Pp. xv + 176, with 35 tables and 48 illustrations, New York, Columbia University Press, 1939, cloth, $3.00.*

By AARON E. MARGULIS

This monograph, number XII of the Columbia Biological Series, edited at Columbia University, is based on the Jessup Lectures given at Columbia University by Doctor Northrop in the spring of 1938. Following an introductory chapter on the general chemistry of enzymes, the book recounts the investigations carried on in Doctor Northrop's laboratory leading to the purification and isolation in crystalline form (for the first time) of the hydrolytic enzymes pepsin, trypsin, chymotrypsin and carboxypeptidase, their precursors pepsinogen, trypsinogen and chymotrypsinogen, and the trypsin-inhibitor substance. In each instance are discussed the methods used in preparation of the crystalline products, all of which, except the trypsin-inhibitor substance, proved to be proteins, the very ingenious tests carried out to prove their purity (Gibbs's phase rule again showing its power) and to indicate the identity of the protein and the active principle, the general properties of the enzyme and pertinent kinetical considerations. The details of the technical methods are summarized in an appendix. The final chapter in the book discusses bacteriophage, included because, although not proved to be an enzyme, there are many points of similarity and, although attempts at its crystallization failed, quite highly active purified concentrates were obtained. Purified phage has the general properties of a nucleoprotein. There is appended a selected bibliography, and an adequate index. The book is attractively designed and printed.

The text is written in a simple, concise style, such that it would be difficult to find a superflous word. Despite this syntactical condensation, the presentation is essentially explanatory and definitive and, except for isolated portions, makes few demands upon the reader's technical knowledge other

than a general knowledge of biology and the basic sciences. The casual reader would certainly not suspect from the restraint of the exposition that the results herein reported are probably the most exciting of the achievements of the application of chemical methods to biology and represent a veritable triumph of twentieth century scientific work. In its implications and in the impetus it has and will give to an ideological synthesis of the living and non-living, its historical counterpart is Wöhler's synthesis of urea more than a century ago. For enzymatic reactions are of the very essence of "vital" phenomena, and yet these remarkable agents, which carry to completion "with rapidity and precision reactions which without them can either not be accomplished at all or only with violent treatment and the expenditure of considerable energy," are finally shown to be rather simple proteins, a result which has long been suspected but denied even eleven years ago by so eminent a chemist as Willstätter.

For the medical reader, this work has specific importance because the enzymes discussed are the proteolytic enzymes of the gastrointestinal tract and several moot problems of the biochemistry of digestion are solved; because it throws new light on the phage and virus problems; and, undoubtedly most important of all, because application of these methods has enabled Stanley to crystallize the virus of tobacco mosaic disease and similar success with other viral agents of disease can be anticipated with all that implies for a most important medical problem.

Proceedings of the National Health Conference, July 18, 19, 20, 1938, Washington, D. C. Interdepartmental Committee to Coördinate Health and Welfare Activities, Josephine Roche, Chairman. Pp. ix + 163, United States Government Printing Office, Washington, 1938, paper, 35 cents.
The Nation's Health. Discussion of the National Health Conference, July 18, 19, 20, 1938, Washington, D. C. Pp. 116, United States Government Printing Office, Washington, 1939, paper, 20 cents.

By MAX PINNER

The discussion reported here took place at the National Health Conference held in Washington, July 18 to 20, 1938. The discussion is based on the report of the Technical Committee on Medical Care, showing the present status and particularly the deficiencies of the present situation (for example, 50,000 more beds for the care of the tuberculous in order to bring the national average up to two beds for every death). The discussants of the Conference represented organized medicine, various medical men not identified with the majority organization, organized labor, an industrial corporation, the insurance field, hospital administrators, public welfare workers, the nursing profession, farming, Parent and Teacher Associations, and women's clubs.

The need for much greater funds would seem obvious, particularly for the medical care of the poorer social strata, many rural areas, preventive medicine and research. On how this need can be filled agreement did not exist, since this question involved principal political and economical ideas, real and imaginary interests and fears, often expressed in standardized taboos and clichees taken from the parlance of political campaigns. How much the medical profession will lead in the development and maintenance of an adequate and humane national health service, or to what extent it will be the unwilling instrument of a governmental program, will probably largely depend on its understanding and acknowledging the existing needs and deficiencies and on the measure of coöperation that it will lend to do the things that must be done. From such point of view the outlook may not be cheering, witness Dr. Morris Fishbein, as spokesman of the American Medical Association, "the problem of medical care is not the most immediate and pressing problem for the American people."—"Let us concern ourselves first with those questions of food, fuel, clothing, shelter, and a job with adequate wages."—"I leave it to you whether or not we [the medical profession] have been called to a conference or whether the patient whom you represent has not asked the medical profession to write a prescription for Radway's Ready Relief, which the patient has written and wants the medical profession to sign so he can get the prescription filled."—On the other hand, Dr. Hugh Cabot, Vice Chairman of the Committee of Physicians for the Improvement of Medical Care, took "the liberty of suggesting that we get over this survey business and get on with the war." As to the survey that the American Medical Association is conducting now, following the report of the Technical Committee on Medical Care, Doctor Cabot said, "I do not myself feel much confidence in the result because I am not clear by precisely what method physicians are to know about the people whom they never see. The people who get no medical care obviously do not crowd the doctors' offices, . . ."

The Nation's Health summarizes concisely the Proceedings and shows clearly the divergent aims, view-points, attitudes—divergent though all based on the acknowledged facts of the present somewhat chaotic state of medical care.

THURMAN B. RICE: *A Textbook of Applied Microbiology and Pathology. Second edition of Applied Bacteriology. Pp. viii + 271, with 76 figures, New York, The Macmillan Company, 1939, fabrikoid, $2.50.*

By SAMUEL ROSEN

This small book was written expressly for the nurse, a fact which might well have been indicated in the title. In his prefatory remarks the author succinctly states the fundamental considerations upon which this textbook is based: "The nurse needs it (bacteriology) so that she may be efficient in sterili-

zation and disinfection, so that she may practice asepsis, isolation, and safe nursing procedure. In addition she must know how to collect and handle specimens for bacteriological examination, and should also be generally intelligent concerning matters relative to the understanding and treatment of disease."

The plan of the book is, in general, similar to that of the usual textbook of bacteriology for medical students. About one-half the text is devoted to general bacteriology and immunology, and the remainder to systematic bacteriology. In the latter section only the more commonly encountered organisms, and the lesions or diseases produced by them, are treated in some detail. Many of those less frequently encountered receive brief mention, however.

In treatment of the subject matter, the author aims at simplicity and clarity of presentation, and emphasis on the practical from the nursing standpoint. This is reflected in the arrangement of the material; the frequent inclusion of common lay terms and expressions, and the use of simple terms along with their scientific equivalents; the employment of apt analogies; and the liberal use of drawings with legends that are instructive rather than merely identifying. The controversial and theoretical are generally avoided, and details of diagnostic procedures and specific treatment are omitted.

The present edition includes a brief section on fundamentals of gross general pathology treated in the same simple manner, and with the same regard for the needs of intelligent nursing as the section on bacteriology.

The author has succeeded in his effort "to present the subject matter in a manner that is interesting and convincing." Typographical errors are relatively few.

ROBERT P. WALTON: *Marihuana—America's New Drug Problem. Pp. ix + 223, with 17 figures, J. B. Lippincott Company, Philadelphia, 1938, cloth, $3.00.*

By J. MASUR

Within recent years increasing reference has been made in newspapers and popular magazines to America's new marihuana menace. Medical literature has paid scant attention to a public health problem that is reputed to be the most important worry of narcotic authorities to-day. The wide-spread prevalence of "reefer" smoking among adolescents with all the train of criminal consequences deserves more interest from our medical conscience.

Synthetic approaches to an artificial paradise are not peculiar to our civilization and marihuana (hashish) shares a long and dishonorable history with other drugs. Of particular sociological significance is the record that the marihuana vice is almost impossible to eradicate once it has become established.

Doctor Walton's comprehensive collection of the available data on marihuana represents a commendable and opportune effort to publicize a new public health danger. It behooves us to learn and to recognize the significance of the odor of burning hay.

WILLIAM MATTHEW CHAMPION: *Medical Information for Social Workers. Contributors: Gerald S. Shibley, Robert L. Faulkner, Maxwell Harbin, M. Paul Motto, John W. Holloway, Herbert B. Wright, I. F. Weidlein, Floyd S. Mowry. Pp. xi + 529, with 25 figures, Baltimore, William Wood & Company, 1938, fabrikoid, $4.00.*

By J. MASUR

Professional social service, particularly the medical variety, has grown up within relatively recent years. The medical information at the command of the trained social worker is often more apparent than factual. The present compendium from the course for social workers at the Western Reserve University makes available certain elementary medical information designed to produce a more intelligent rapport between social worker and physician. Despite the difficult premise of presenting descriptions of disease and generalizations concerning prognoses, the book is a well worth while acquisition for social workers desirous of obtaining a better understanding of patients and medical practice. Unfortunately space limitations in such a comprehensive survey did not permit more emphasis on the medical-social components, especially from the point of view of chronic disease. The sections on venereal diseases are extremely good. The bibliography deserves careful revision in subsequent editions.

ERWIN SCHLIEPHAKE: *Short-Wave Therapy. The Medical Uses of Electrical High Frequencies. Second English edition, translated by R. King Brown. Pp. 296 + 24, with 148 illustrations, The Actinic Press, Ltd., London, 1938, cloth, 21/—net.*

By K. HARPUDER

Dr. E. Schliephake, one of the fathers of the medical use of short-wave machines, presents in the first chapters of his book an outline of the physics of high frequency currents which is followed by an extensive report on their biological effects. The next hundred pages are devoted to short-wave therapy of human diseases.

The physical part describes comprehensively the more pertinent facts for

the physician. In the biological parts, the author attempts to show the peculiar heat effects of short-wave currents in electrolyte and colloidal solutions, in bacteria, in tissues, in animals and in the human body. The question of specific—other than heat—effects is left open. Sometimes less important material is reported or doubtful and disproved experiments are quoted without criticism.

The clinical section of the book enumerates many diseases in which short-wave therapy is helpful or even curative. The necessity of choosing the proper wave length and of proper applications is repeatedly emphasized. No rules and no reasons are, however, established. The discrepancy between the results of the author and those obtained by American physicians is obviously great. In pulmonary diseases good effects are reported for "not too advanced" cases of bronchiectasis, in proliferative fibrotic tuberculosis, in pleural effusions, in pleural empyema and in pulmonary abscess and gangrene. In 45 cases of "lung abscesses or other purulent conditions of the lungs" 42 complete cures and 3 fatal results are reported, the latter "in any event hopeless cases." A case of glioma of the vermiform process is described (page 118) which, unsuccessfully operated and treated with radium, was exposed to 15 m., 6 m. and 4 m. short-wave therapy. The first relieved cerebral pressure and after the latter two "the patient is improved today to such an extent that one could hardly have believed it possible."

The translation by R. King Brown is full of Germanisms and unusual expressions, like "voracity of leucocytes" (phagocytosis) or "concentrated chain" (concentration cell). Numerous typographical errors render reading still more difficult.

Brief Comment

SOL ROY ROSENTHAL: *The General Tissue and Humoral Response to an Avirulent Tubercle Bacillus. Pp. 184, with 1 plate, 80 figures and 23 charts, The University of Illinois Press, Urbana, 1938, cloth, $3.00.*

This is an extensive study, elaborately presented, of the relatively small subject of the response of guinea pigs to the introduction of various amounts, and by various routes, of BCG, and of the fate of the bacilli so administered. As a whole, these studies are a confirmation and elaboration of data available in the voluminous literature on this subject. It is important that the few isolated reports on the derivation of pathogenic dissociates from BCG could not be confirmed. The most interesting finding is probably the generalized proliferative response of the reticuloendothelial cells to the administration of BCG which occurred regardless of the portal of entry. However, Doctor Rosenthal's statement that this generalized reaction is attributable to "sub-

microscopic" bacillary forms (something standing between the generally acknowledged granula and the still hypothetical "ultravirus" of the French authors) is not too convincing, particularly since qualitatively similar reticulo-endothelial responses can be elicited by nonspecific foreign bodies and by certain chemical fractions of tubercle bacilli.

This monograph is profusely illustrated by well executed photomicrographs.

The literature is apparently not always handled too carefully: that Kahn has demonstrated filtrable forms of the tubercle bacillus and that Much considered the granula he described as degenerative forms is incorrect.

PHILIP KLEIN AND MARY R. BAKER: *A Program for the Care of Jewish Tuberculous. Report to the Joint Committee on the Study of the Institutions and Programs for the Care of the Jewish Tuberculous. Pp. 119, 1938, paper.*

This is a thorough and understanding study of the subject indicated in the title. In refreshing contrast to some other committee reports, this essay is a direct and honest investigation whose frankness in showing faults and deficiencies is most commendable, particularly since the critique is always constructive and never aggressive. This report contains a good deal of solid information and significant suggestions that are of interest to many workers in tuberculosis who are not specifically concerned with sectarian institutions, such as the discussion of fully integrated tuberculosis services and the existing lack of and profound need for sound systems of after-care and economic rehabilitation.

CH. BRODY (with 28 collaborators): *Traité d'hélio- et d'actinologie. Volumes 1 and 2. Pp. viii + 1502, with 618 figures and 42 tables, Librairie Maloine, Paris, 1938, paper, 440 fr.*

An excellent French encyclopaedic treatise on heliotherapy, which will be reviewed more fully in the next book review section in *The American Review of Tuberculosis.*

Books Received

HERNAN D. AGUILAR: La Toracoplastia en el tratamiento de la tuberculosis pulmonar. Volumes 1 and 2. Pp. xxv + 1504, with 217 figures, Libreria y Editorial "El Ateneo," Buenos Aires, 1938, paper.

NOEL DEAN BARDSWELL: Tuberculosis in Cyprus. An Interim Report on Its Incidence and Means of Control. Pp. vi + 228, with many illustrations, London, printed for the National Association for the Prevention of Tuberculosis by Adlard & Son, Limited, 1937, paper.

C. M. DESVERNINE Y GALDOS: Estudio de ciertos aspectos de la sintomatología muscular, funcional, en la tuberculosis pulmonar crónica. Pp. 43, with 14 figures, La Habana Imprenta "El Siglo XX," A Muniz y Hno., Brasil, 153 al 157, 1939, paper.

Handbook of Tuberculosis Schemes for Great Britain and Ireland. Tenth edition. Pp. iv + 200, National Association for the Prevention of Tuberculosis, London, 1939, paper.

OTTO JÜNGLING: Allgemeine Strahlentherapie; Licht, Röntgenstrahlen, Radium. Pp. xii + 323, with 136 illustrations, Ferdinand Enke Verlag, Stuttgart, 1938, paper, RM. 22.80.

The Papworth Village Settlement. Report of the Committee of Management and Medical Director for 1937, presented at the twenty-first annual general meeting of the Settlement, July 12, 1938. Pp. 56, with numerous photographs, Papworth, 1938, paper.

WALTER PRYLL: Economical Administration of Health Insurance Benefits. Part I. The Principle of Economy in the Administration of Health Benefits. Pp. 137, International Labour Office, Geneva, 1938, paper.

Report of the Medical Research Council for the year 1937–1938. Committee of the Privy Council for Medical Research. Pp. 221 + xvi, London, His Majesty's Stationery Office, 1939, paper, 3s. 6d.

Silicosis and Asbestosis. Edited by A. J. Lanza. Contributors: A. J. Lanza, R. R. Sayers, Eugene P. Pendergrass, S. Roodhouse Gloyne, Leroy U. Gardner and E. L. Middleton. Pp. xxvi + 439, with 60 illustrations, Oxford University Press, New York, 1938, cloth, $4.25. (To be reviewed later.)

FOLLOW-UP STUDY OF TUBERCULOUS PATIENTS[1,2]

On Patients Discharged from a County Sanatorium

D. R. HASTINGS AND ESTHER R. DOERR

At no time in the history of the control of tuberculosis has there been a greater need than there is to-day for an evaluation of methods of treatment and care of the tuberculous patient. Although tuberculosis is on the decline, the death rate in Minnesota for all of its forms, when plotted on semi-logarithmic paper, would seem to show a slighter rate of decrease in the last few years. Some no doubt would believe we are reaching an irreducible minimum. This residue of some 30 persons out of every 100,000 exists after our present methods of control and treatment are used. To conquer this stubborn fragment those efforts put forth yesterday and to-day must be studied with the idea of discovering what measures are most effective and where the program is lacking.

It is with this idea in mind that Glen Lake Sanatorium for some years has attempted to keep in contact with those of its patients who have been discharged. The Sanatorium was fortunate this year to be included in a state-wide Works Progress Administration project to study mortality experience and condition after hospitalization on tuberculosis patients discharged from Minnesota sanatoria. Dr. H. E. Hilleboe, Director of the Division of Tuberculosis of the State Board of Control, supervised the project (1). The work on the Glen Lake patients was carried on in the Out-Patient Department of the Sanatorium where the follow-up data are recorded. The information was typed on a tabulating card and the cards punched by W. P. A. workers. For checking purposes two cards were typed and punched for each case by different workers. After comparison, one card was sent to the State Board of Control and one kept in the out-patient office.

The information available on the patients comes from a variety of sources. Many of the cases report to one of the several chest clinics

[1] From the Out-Patient Department of Glen Lake Sanatorium, Oak Terrace, Minnesota, and the Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

[2] Recognition is hereby given to the Works Progress Administration for workers for transcription and punching furnished on Project No. 165-71-7264.

maintained by the Glen Lake Sanatorium Out-Patient Department for those who are financially unable to consult a private physician. Those who do not attend clinic are contacted by mail and, if they state they have seen a physician, their doctor is asked to fill out and return a medical card. The vital statistics in the local newspapers are scanned daily for names of ex-patients. All untraced cases at the time of the study were checked with the State Board of Health files and with the confidential central registry of the State Board of Control, which provides information on all persons receiving public assistance and those in penal and custodial institutions in Minnesota.

Because the Sanatorium was first opened in 1916, it was decided to divide the study into two ten-year periods, the first including those discharged from 1916 to 1925, and the second from 1926 to 1935. Since the greater part of the study was carried on in 1937, this allowed at least one year's follow-up for each patient.

It would be complicated to attempt an analysis of all forms of tuberculosis in one paper; and the relatively few cases available for study in childhood and extrapulmonary tuberculosis do not justify the drawing of conclusions. Therefore, it was deemed advisable to limit the study to those with adult type of pulmonary tuberculosis. Also, the study includes only white individuals and those hospitalized for at least ninety days, it being felt that not a great deal of benefit could be derived from a stay of less than this time. Of necessity, the single discharges are separated from the multiple discharges and only the single ones dealt with here.

Table 1 summarizes the discharges for the period 1916 to 1925, and table 2 for the years 1926 to 1935 inclusive. It is interesting to note the marked differences in the two groups. Of the 1,072 cases in the first group, 13.3 per cent were classified as minimal, 31.1 per cent as moderately advanced, and 55.6 per cent as far advanced. In the group discharged from 1926 to 1935, 9.4 per cent were minimal, 27.8 per cent moderately advanced, and 62.9 per cent far advanced. In spite of the increased proportion of far advanced cases in the later group the percentage dead on discharge was 36.3 as compared with 42.6 in the first group. Of those discharged alive, 33 per cent of the early group had more than one discharge or were hospitalized for a period of less than ninety days, while only slightly less, 29.8 per cent, of the later group came in this category. Eliminating these cases, we find that of the number to be studied 21.1 per cent of the 1916 to 1925 group and 7.1 per cent of

the 1926 to 1935 group were not traced after discharge. The remaining cases show that the average length of hospitalization for group 1 was 1.1 years as compared with 2.1 years for group 2. It is a significant fact that 51.7 per cent of the first group died after discharge as compared with 20.2 per cent of the second group. Since the first group was followed

TABLE 1

White persons discharged from Glen Lake Sanatorium according to stage of disease on discharge, 1916–1925

	STAGE OF DISEASE ON DISCHARGE			
	Minimal	Moderately advanced	Far advanced	Total
Total cases discharged	143	333	596	1,072
Dead on discharge	8	70	379	457
Under ninety days' stay or more than one discharge	37	81	85	203
Untraced	27	40	20	87
Total cases used in study	71	142	112	325
Dying after discharge	8	68	92	168
Living last report	63	74	20	157

TABLE 2

White persons discharged from Glen Lake Sanatorium according to stage of disease on discharge, 1926–1935

	STAGE OF DISEASE ON DISCHARGE			
	Minimal	Moderately advanced	Far advanced	Total
Total cases discharged	274	811	1,837	2,922
Dead on discharge	12	101	949	1,062
Under ninety days' stay or more than one discharge	67	185	302	554
Untraced	11	44	38	93
Total cases used in study	184	481	548	1,213
Dying after discharge	9	82	154	245
Living last report	175	399	394	968

over a longer period of years, they would be exposed to the risk of dying over a greater period. However, it is generally held that the greatest mortality rate is expected in the first five years following hospitalization. This no doubt is partly responsible for the low average number of 7.8 years that the group was followed. One would expect a number larger than this, for theoretically in 1936 the group discharged from 1916 to

1925 would have been followed on the average for a period of about fifteen years. The second group was followed for an average of 4.5 years in comparison with the theoretical approximate of five years.

Changes in diagnostic standards and methods of treatment, variance in the length of hospitalization and length of time followed, and the difference in the percentage of deaths made it advisable to confine a detailed study to those discharged between 1926 and 1935. Also, the greater number of cases appear in this group owing to an increase in bed capacity in the years 1925 and 1927. As a result the following tables and discussion will deal almost exclusively with the 1,213 white patients with adult type of pulmonary tuberculosis discharged alive during this period

TABLE 3

Age and sex according to stage of disease on discharge, 1926–1935

AGE	MINIMAL				MODERATELY ADVANCED				FAR ADVANCED				TOTAL			
	Male	Female	Total	Per cent	Male	Female	Total	Per cent	Male	Female	Total	Per cent	Male	Female	Total	Per cent
years																
5–14	1	6	7	3.8	1	3	4	0.8	1	0	1	0.2	3	9	12	1.0
15–24	15	32	47	25.6	21	76	97	20.2	31	61	92	16.8	67	169	236	19.5
25–34	17	59	76	41.3	73	130	203	42.2	92	131	223	40.7	182	320	502	41.4
35–44	9	17	26	14.1	32	50	82	17.0	53	60	113	20.6	94	127	221	18.2
45–54	12	4	16	8.7	34	27	61	12.7	50	24	74	13.5	96	55	151	12.4
55–64	4	4	8	4.3	14	11	25	5.2	17	14	31	5.7	35	29	64	5.3
65+	3	1	4	2.2	6	3	9	1.9	12	2	14	2.5	21	6	27	2.2
Total...	61	123	184	100.0	181	300	481	100.0	256	292	548	100.0	498	715	1,213	100.0

after only one hospitalization of not less than ninety days and traced after discharge.

If a study is to be made of the mortality experience and condition after discharge on sanatoria patients, the status of these patients on discharge must be known and thoroughly kept in mind when interpreting future results. From this standpoint the following figures are presented.

The 1,213 patients studied consist of 184, or 15.2 per cent, minimal cases, 481, or 39.6 per cent, with moderately advanced tuberculosis, and 548, or 45.2 per cent, with the disease in the far advanced stage. Table 3 gives the distribution of the cases by age, sex and classification of disease. The age distribution for the general population of Minnesota at the time of the 1930 census was 20 per cent for five to fourteen years, 18 per

cent for fifteen to twenty-four years, 15 per cent for twenty-five to thirty-four years, 14 per cent for thirty-five to forty-four years, 10 per cent for forty-five to fifty-four years, 7 per cent for fifty-five to sixty-four years, and 6 per cent for sixty-five years and over. The percentage of discharged cases falling in the age group twenty-five to thirty-four years is considerably greater than for the general population, reflecting the high incidence of tuberculosis in this age group.

As stated previously the average length of hospitalization for the total 1,213 cases was 2.1 years. As would be expected, the minimal cases had the shortest residence with 1.3 years, then the moderately advanced cases with 2.0 years, and the far advanced with the longest hospital stay, or 2.4 years.

TABLE 4

Condition on discharge according to stage of disease on discharge, 1926–1935

CONDITION ON DISCHARGE	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Not noted	—	—	1	0.2	—	—	1	0.1
Arrested	104	56.5	159	33.1	179	32.7	442	36.4
Apparently arrested	26	14.2	68	14.1	42	7.7	136	11.2
Quiescent	19	10.3	81	16.8	90	16.4	190	15.7
Improved	33	17.9	144	30.0	157	28.6	334	27.5
Unimproved	2	1.1	28	5.8	80	14.6	110	9.1
Total	184	100.0	481	100.0	548	100.0	1,213	100.0

Of much more significance than the length of hospitalization is the condition on discharge. A patient who remains in the hospital long enough to become an arrested case would seem to have a better outlook than one who leaves the sanatorium before the disease has become arrested. In table 4 are presented the cases studied by stage of disease and condition on discharge. Of those whose condition was quiescent or better, 81.0 per cent were minimal cases, 64.2 per cent moderately advanced, and only 56.8 per cent far advanced, or an average of 63.4 per cent for the three classifications of the disease. This leaves in the improved and unimproved group 19.0 per cent of the minimal, 35.8 per cent of the moderately advanced, 43.2 per cent of the far advanced, and 36.6 per cent of all stages of disease. This again emphasizes the importance of an early diagnosis if the disease is to become arrested.

No doubt another factor which influences the mortality of the dis-

charged patient is the status of the sputum on discharge. A patient was considered to have positive sputum on discharge if the examination had shown the presence of tubercle bacilli within three months prior to the end of hospitalization. The Ziehl-Neelsen method was used to determine the presence of the bacilli, and cases giving negative results were checked by a culture or guinea pig test if requested by the staff physician. The proportion of cases in each stage having a positive sputum on discharge is shown in table 5. It is noticeable that the per-

TABLE 5

Condition of sputum on discharge according to stage of disease on discharge, 1926–1935

CONDITION OF SPUTUM	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Positive	2	1.1	40	8.3	128	23.4	170	14.0
Negative	182	98.9	441	91.7	420	76.6	1,043	86.0
Total	184	100.0	481	100.0	548	100.0	1,213	100.0

TABLE 6

Extrapulmonary tuberculosis complications according to stage of disease on discharge, 1926–1935

EXTRAPULMONARY TUBERCULOSIS	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Cervical adenitis only	6	3.2	6	1.3	4	0.7	16	1.3
Bone and joint only	2	1.1	13	2.7	20	3.7	35	2.9
Gastrointestinal only	2	1.1	29	6.0	55	10.0	86	7.1
Laryngeal only	0	0.0	16	3.3	34	6.2	50	4.1
Combinations and others	23	12.5	71	14.8	109	19.9	203	16.7
None	151	82.1	346	71.9	326	59.5	823	67.9
Total	184	100.0	481	100.0	548	100.0	1,213	100.0

centage among the minimal is negligible and increases to about one-fourth among the far advanced cases.

It should also be borne in mind that there would appear forms of extrapulmonary tuberculosis coexisting with the adult type of pulmonary tuberculosis. Table 6 shows that various combinations of extrapulmonary tuberculosis were found in 12.5 per cent of the minimal, 14.8 per cent of the moderately advanced, and 19.9 per cent of the far advanced pulmonary cases. No extrapulmonary tuberculosis was found com-

plicating 82.1 per cent of the minimal, 71.9 per cent of the moderately advanced, and 59.5 per cent of the far advanced cases. Cervical adenitis, bone and joint, gastrointestinal and laryngeal tuberculosis appeared as single complications in the remaining cases. It would seem probable that those having to combat only a pulmonary condition would experience a lower mortality rate than those with extrapulmonary complications.

Of unusual interest to both the patient and the physician is the result of collapse therapy on the mortality of the discharged patient. From table 7 it is noted that almost no minimal cases were given special treatment to collapse the lung while better than one-third of the moderately advanced and almost one-half of the far advanced cases had received some form of pulmonary collapse.

TABLE 7

Type of collapse treatment during residence according to stage of disease on discharge, 1926–1935

TYPE OF COLLAPSE TREATMENT DURING RESIDENCE	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Pneumothorax only	2	1.1	104	21.6	136	24.8	242	19.9
Phrenic surgery only	4	2.2	14	2.9	23	4.2	41	3.4
Thoracoplasty only	0	0.0	5	1.1	12	2.2	17	1.4
More than one type	3	1.6	54	11.2	93	17.0	150	12.4
No collapse treatment	175	95.1	304	63.2	284	51.8	763	62.9
Total	184	100.0	481	100.0	548	100.0	1,213	100.0

The method of study used to interpret data compiled on patients discharged from Glen Lake Sanatorium was the life-table analysis outlined by Dr. W. H. Frost (2). This method enables one to compare the mortality experience of the discharged patients with that of individuals in the general population. The basic unit of measurement is one person followed one year or one person-year of life experience. Since the death rate for tuberculosis varies in different ages, the rates computed must be age-specific rates. The deaths occurring among discharged patients of a certain age group can be compared with the number you would expect if the rate prevalent in the general population for that group functioned on the person-years of experience contributed by it.

In the subsequent tables this method of life-table analysis is used to study the mortality of the discharged patients by stage of disease alone

and then cognizance is taken of such factors as condition on discharge, sputum on discharge and collapse therapy treatment given. In many instances the numbers are so small that the results cannot present a true

TABLE 8

Mortality from all causes and tuberculosis by age and stage of disease, 1916–1925

STAGE OF DISEASE	AGE	PERSON-YEARS OF LIFE EXPERIENCE	TUBERCULOSIS			ALL CAUSES			
			Deaths	Minnesota death rate per 100,000 population, 1920*	Expected deaths	Deaths	Annual death rate per 1,000 person-years†	Minnesota death rate per 1,000 population, 1920*	Expected deaths
	years								
Minimal (71 cases)	5–14	6.5	0	21.76	0.00	0	—	2.25	0.01
	15–24	85.0	1	104.68	0.09	1	—	3.93	0.33
	25–34	335.5	2	146.50	0.49	2	5.96	6.17	2.07
	35–44	297.5	1	125.04	0.37	1	3.36	6.70	1.99
	45–54	117.5	0	87.42	0.10	2	17.02	9.69	1.14
	55+	63.0	1	110.81	0.07	2	31.75	40.54	2.55
	Total	905.0	5	89.82	1.12	8	8.84‡	10.60	8.09
Moderately advanced (142 cases)	5–14	6.5	1	21.76	0.00	1	—	2.25	0.01
	15–24	55.5	9	104.68	0.06	10	—	3.93	0.22
	25–34	415.5	23	146.50	0.61	27	64.98	6.17	2.56
	35–44	384.5	15	125.04	0.48	20	52.02	6.70	2.58
	45–54	199.0	1	87.42	0.17	3	15.08	9.69	1.93
	55+	130.0	3	110.81	0.14	7	53.85	40.54	5.27
	Total	1,191.0	52	89.82	1.46	68	57.09‡	10.60	12.57
Far advanced (112 cases)	5–14	1.5	1	21.76	0.00	1	—	2.25	0.00
	15–24	18.0	19	104.68	0.02	19	—	3.93	0.07
	25–34	161.5	40	146.50	0.24	41	253.87	6.17	1.00
	35–44	129.5	20	125.04	0.16	20	—	6.70	0.87
	45–54	62.0	4	87.42	0.05	5	—	9.69	0.60
	55+	51.5	6	110.81	0.06	6	116.50	40.54	2.09
	Total	424.0	90	89.82	0.53	92	216.98‡	10.60	4.63

* From U. S. Mortality Statistics 1920.

† Not calculated for tuberculosis because of insufficient person-years to expect one death.

‡ Not comparable due to differences in age distribution.

picture; certain trends are indicated and the figures are given with the idea that persons having comparable data might combine the work to study it for conclusions on a wider scale. It was felt that in cases where the person-years of experience were too few to ordinarily expect

one death if the rates for the general population were in force, the number was too small to be significant.

TABLE 9

Mortality from all causes and tuberculosis by age and stage of disease, 1926–1935

STAGE OF DISEASE	AGE	PERSON-YEARS OF LIFE EXPERIENCE	TUBERCULOSIS			ALL CAUSES			
			Deaths	Minnesota death rate per 100,000 population, 1930*	Expected deaths	Deaths	Annual death rate per 1,000 person-years†	Minnesota death rate per 1,000 population, 1930*	Expected deaths
	years								
Minimal (184 cases)	5–14	15.0	0	8.62	0.00	0	—	1.54	0.02
	15–24	145.5	0	47.54	0.07	0	—	2.53	0.37
	25–34	369.0	0	73.07	0.27	0	—	3.49	1.29
	35–44	214.0	1	65.32	0.14	2	9.35	5.30	1.13
	45–54	104.0	1	63.87	0.07	3	28.85	9.76	1.02
	55+	67.5	2	69.69	0.05	4	59.26	41.98	2.83
	Total	915.0	4	48.67	0.60	9	9.84‡	10.02	6.66
Moderately advanced (481 cases)	5–14	11.5	0	8.62	0.00	0	—	1.54	0.02
	15–24	196.5	9	47.54	0.09	9	—	2.53	0.50
	25–34	993.5	23	73.07	0.73	30	30.20	3.49	3.47
	35–44	605.0	11	65.32	0.40	14	23.14	5.30	3.21
	45–54	335.5	7	63.87	0.21	12	35.77	9.76	3.27
	55+	186.0	8	69.69	0.13	17	91.40	41.98	7.81
	Total	2,328.0	58	48.67	1.56	82	35.22‡	10.02	18.28
Far advanced (548 cases)	5–14	0.0	1	8.62	0.00	1	—	1.54	0.00
	15–24	160.5	13	47.54	0.08	13	—	2.53	0.41
	25–34	904.0	40	73.07	0.66	43	47.57	3.49	3.15
	35–44	607.0	34	65.32	0.40	43	70.84	5.30	3.22
	45–54	358.5	26	63.87	0.23	31	86.47	9.76	3.50
	55+	235.0	18	69.69	0.16	23	97.87	41.98	9.87
	Total	2,265.0	132	48.67	1.53	154	67.99‡	10.02	20.15

* From U. S. Mortality Statistics 1930.

† Not calculated for tuberculosis because of insufficient person-years to expect one death.

‡ Not comparable due to differences in age distribution.

Tables 8 and 9 present the experience of the patients discharged from 1916 to 1925 and from 1926 to 1935 respectively. While the number of person-years of experience is small in the group discharged between 1916 and 1925, it is of interest to note that the ratio of actual to expected

deaths for all causes is 1.0 in the minimal group, 5.4 in the moderately advanced and 19.9 in the far advanced cases. For those discharged from 1926 to 1935 inclusive the ratio of the actual to the expected deaths for all age groups is 1.4 for the minimal, 4.5 for the moderately advanced and 7.6 among the far advanced. That is, the white person with minimal tuberculosis, discharged only once from Glen Lake Sanatorium between 1926 and 1935 after a residence of at least ninety days, has his chances

TABLE 10

Mortality from all causes by age and condition on discharge for moderately advanced cases, 1926–1935

CONDITION ON DISCHARGE	AGE	PERSON-YEARS OF LIFE EXPERIENCE	DEATHS	ANNUAL DEATH RATE PER 1,000 PERSON-YEARS*	MINNESOTA DEATH RATE PER 1,000 POPULATION, 1930	EXPECTED DEATHS	RATIO ACTUAL TO EXPECTED DEATHS
	years						
Arrested and apparently arrested (228 cases)	5–14	11.5	0	—	1.54	0.02	—
	15–24	101.0	0	—	2.53	0.26	—
	25–34	458.5	4	8.72	3.49	1.60	2.50
	35–44	264.0	3	11.36	5.30	1.40	2.14
	45–54	171.0	4	23.39	9.76	1.67	2.40
	55+	92.0	5	54.35	41.98	3.86	1.30
	Total	1,098.0	16	14.57	10.02	8.81	—
Quiescent, improved and unimproved (253 cases)	5–14	0.0	0	—	1.54	0.00	—
	15–24	95.5	9	—	2.53	0.24	—
	25–34	535.0	26	48.60	3.49	1.87	13.90
	35–44	341.0	11	32.26	5.30	1.81	6.08
	45–54	164.5	8	48.63	9.76	1.61	4.97
	55+	94.0	12	127.66	41.98	3.95	3.04
	Total	1,230.0	66	53.66	10.02	9.48	—

* When adjusted for differences in age distribution the rate is 15.80 for the arrested and apparently arrested group and 50.88 for the quiescent, improved and unimproved group. These adjusted rates are based only on those age groups with sufficient person-years of life experience to ordinarily expect one death if the rates for the general population were in force.

of dying in the first five years after discharge increased 1.4 times over those persons present in the general population of Minnesota at the time of the 1930 census. Likewise, the mortality risk of the moderately advanced cases is 4.5 times and the far advanced 7.6 times that of the normal Minnesota population.

It must be borne in mind that a direct comparison of the ratios of total

actual to expected deaths cannot be made between the three classifications of disease due to differences in age distribution. To correct for these differences a standard population composed of the combined person-years of life experience for all stages of disease was employed. The rates based on actual deaths occurring in the various age groups in each stage were used on the combined person-years of experience to ascertain the number of deaths that would occur. The total deaths were then

TABLE 11

Mortality from all causes by age and condition on discharge for far advanced cases, 1926–1935

CONDITION ON DISCHARGE	AGE	PERSON-YEARS OF LIFE EXPERIENCE	DEATHS	ANNUAL DEATH RATE PER 1,000 PERSON-YEARS*	MINNESOTA DEATH RATE PER 1,000 POPULATION, 1930	EXPECTED DEATHS	RATIO ACTUAL TO EXPECTED DEATHS
	years						
Arrested and apparently arrested (221 cases)	5–14	0.0	0	—	1.54	0.00	—
	15–24	79.5	0	—	2.53	0.20	—
	25–34	397.0	2	5.04	3.49	1.39	1.44
	35–44	220.0	5	22.73	5.30	1.17	4.27
	45–54	153.5	6	39.09	9.76	1.50	4.00
	55+	123.0	4	32.52	41.98	5.16	0.78
	Total	973.0	17	17.47	10.02	9.42	—
Quiescent, improved and unimproved (327 cases)	5–14	0.0	1	—	1.54	0.00	—
	15–24	81.0	13	—	2.53	0.20	—
	25–34	507.0	41	80.87	3.49	1.77	23.16
	35–44	387.0	38	98.19	5.30	2.05	18.54
	45–54	205.0	25	121.95	9.76	2.00	12.50
	55+	112.0	19	169.64	41.98	4.70	4.04
	Total	1,292.0	137	106.04	10.02	10.72	—

* When adjusted for differences in age distribution the rate is 19.01 for the arrested and apparently arrested group and 102.78 for the quiescent, improved and unimproved group. These adjusted rates are based only on those age groups with sufficient person-years of life experience to ordinarily expect one death if the rates for the general population were in force.

compared with the deaths expected if the rates for the general population were in force. Only those age groups with rates appearing in tables 8 and 9 were used; the others were felt to be unreliable because of insufficient person-years to expect one death. When this method is employed on those persons discharged from 1916 to 1925 inclusive the ratio of actual to expected deaths is 0.9 for the minimal, 4.7 for the moderately advanced and 16.1 for the far advanced cases. In the group discharged

from 1926 to 1935 inclusive the ratio is 1.5 for the minimal, 4.0 for the moderately advanced and 7.4 for the far advanced cases. It must also be borne in mind that the two ten-year periods are not directly comparable due to differences in age distribution, length of hospitalization, condition on discharge, treatment given, etc.

It was pointed out previously that such factors as condition on discharge, sputum on discharge and collapse therapy treatment may be

TABLE 12

Mortality from all causes by age, condition of sputum and stage of disease on discharge, 1926–1935

STAGE OF DISEASE	AGE	POSITIVE SPUTUM		NEGATIVE SPUTUM					RATIO ACTUAL TO EXPECTED DEATHS	
		Person-years of life experience	Deaths	Person-years of life experience	Deaths	Annual death rate per 1,000 person-years	Minnesota death rate per 1,000 population, 1930	Expected deaths	Negative	All cases
	years									
Moderately advanced	5–14	0.0	0	11.5	0	—	1.54	0.02	—	—
	15–24	17.5	6	179.0	3	—	2.53	0.45	—	—
	25–34	70.5	9	923.0	21	22.75	3.49	3.22	6.52	8.65
	35–44	47.5	5	557.5	9	16.14	5.30	2.95	3.05	4.36
	45–54	12.5	2	323.0	10	30.96	9.76	3.15	3.17	3.67
	55+	8.0	2	178.0	15	84.27	41.98	7.47	2.01	2.18
	Total	156.0	24	2,172.0	58	26.70*	10.02	17.26	—	—
Far advanced	5–14	0.0	1	0.0	0	—	1.54	0.00	—	—
	15–24	14.5	9	146.0	4	—	2.53	0.37	—	—
	25–34	126.0	31	778.0	12	15.42	3.49	2.72	4.41	13.65
	35–44	96.5	25	510.5	18	35.26	5.30	2.71	6.64	13.35
	45–54	51.5	16	307.0	15	48.86	9.76	3.00	5.00	8.86
	55+	16.5	9	218.5	14	64.07	41.98	9.17	1.53	2.33
	Total	305.0	91	1,960.0	63	32.14*	10.02	17.97	—	—

* Not comparable due to differences in age distribution.

expected to have a bearing on the mortality of the discharged patient; accordingly the character of the 1,213 cases in this study were described. An attempt has been made to evaluate these factors by method of the life-table analysis. The analysis is confined to the moderately and far advanced cases because there were relatively few minimal cases discharged as only quiescent, or with a positive sputum, or having collapse therapy treatment.

In table 10 is presented a life-table analysis of the 481 moderately advanced cases divided into two groups according to condition on discharge. Likewise table 11 shows an analysis of the 548 cases in the far advanced stage. Of interest is the comparison of the ratios of the actual to expected deaths from all causes in the group discharged as arrested or apparently arrested and those discharged as only quiescent, improved or unimproved. As would be natural to expect, the arrested

TABLE 13

Mortality from all causes by age and collapse therapy for moderately advanced cases, 1926–1935

COLLAPSE THERAPY PRIOR TO DISCHARGE	AGE	PERSON-YEARS OF LIFE EXPERIENCE	DEATHS	ANNUAL DEATH RATE PER 1,000 PERSON-YEARS*	MINNESOTA DEATH RATE PER 1,000 POPULATION, 1930	EXPECTED DEATHS	RATIO ACTUAL TO EXPECTED DEATHS
	years						
With collapse treatment (177 cases)	5–14	2.0	0	—	1.54	0.00	—
	15–24	82.0	5	—	2.53	0.21	—
	25–34	397.5	12	30.19	3.49	1.39	8.63
	35–44	192.5	3	15.58	5.30	1.02	2.94
	45–54	70.5	2	—	9.76	0.69	—
	55+	25.5	2	78.43	41.98	1.07	1.87
	Total	770.0	24	31.20	10.02	4.38	—
Without collapse treatment (304 cases)	5–14	9.5	0	—	1.54	0.01	—
	15–24	114.5	4	—	2.53	0.29	—
	25–34	596.0	18	30.20	3.49	2.08	8.65
	35–44	412.5	11	26.67	5.30	2.19	5.02
	45–54	265.0	10	37.74	9.76	2.59	3.86
	55+	160.5	15	93.46	41.98	6.74	2.23
	Total	1,558.0	58	37.23	10.02	13.90	—

* When adjusted for differences in age distribution the rate is 30.27 for the group with collapse treatment and 35.60 for the group without collapse treatment. These adjusted rates are based only on those age groups with sufficient person-years of life experience to ordinarily expect one death if the rates for the general population were in force.

group shows a smaller ratio of actual to expected deaths in each age group, especially in the far advanced stage of the disease. The length of time the patients were followed is essentially the same for the two groups. In the moderately advanced cases the average length of time followed was 4.8 years for the arrested group and 4.9 years for those with a less favorable condition on discharge. Likewise the far advanced group showed 4.4 years of follow-up experience in the first group and 4.0 years in the second group.

Since there were comparatively few individuals discharged with a positive sputum, the negative sputum group was compared with the combined group. The data for this comparison will be found in table 12. While this is not a direct comparison, it would almost appear from the ratios that in the far advanced cases those with a negative sputum experienced a somewhat lower mortality rate than the group as a whole. As in the case of condition on discharge, the length of time followed was

TABLE 14

Mortality from all causes by age and collapse therapy for far advanced cases, 1926–1935

COLLAPSE THERAPY PRIOR TO DISCHARGE	AGE	PERSON-YEARS OF LIFE EXPERIENCE	DEATHS	ANNUAL DEATH RATE PER 1,000 PERSON-YEARS*	MINNESOTA DEATH RATE PER 1,000 POPULATION, 1930	EXPECTED DEATHS	RATIO ACTUAL TO EXPECTED DEATHS
	years						
With collapse treatment (264 cases)	5–14	0.0	0	—	1.54	0.00	—
	15–24	122.0	1	—	2.53	0.31	—
	25–34	504.0	10	19.84	3.49	1.76	5.68
	35–44	291.5	12	41.17	5.30	1.54	7.79
	45–54	141.0	8	56.74	9.76	1.38	5.80
	55+	44.5	5	112.36	41.98	1.87	2.67
	Total	1,103.0	36	32.64	10.02	6.86	—
Without collapse treatment (284 cases)	5–14	0.0	1	—	1.54	0.00	—
	15–24	38.5	12	—	2.53	0.10	—
	25–34	400.0	33	82.50	3.49	1.40	23.57
	35–44	315.5	31	98.26	5.30	1.67	18.56
	45–54	217.5	23	105.75	9.76	2.12	10.85
	55+	190.5	18	94.49	41.98	8.00	2.25
	Total	1,162.0	118	101.55	10.02	13.29	—

* When adjusted for differences in age distribution the rate is 42.61 for the group with collapse treatment and 92.34 for the group without collapse treatment. These adjusted rates are based only on those age groups with sufficient person-years of life experience to ordinarily expect one death if the rates for the general population were in force.

similar for the two groups, being somewhat shorter for the combined group.

In table 13 is presented the mortality experience of the moderately advanced cases according to whether or not they had received collapse therapy treatment prior to discharge. Here again, as in the case of sputum on discharge, the moderately advanced cases show nothing highly significant. This may be attributed to the fact that in the moderately advanced stage of the disease those cases given collapse therapy represent

a group having more constitutional symptoms than those without chest surgery.

Table 14 gives the corresponding information on the far advanced cases. In this stage of the disease those with collapse therapy appear to have a more favorable after-history than those without chest surgery, especially in the age group twenty-five to thirty-four.

SUMMARY

Statistics have been presented on the 3,994 patients discharged from Glen Lake Sanatorium from the time of its opening in 1916 through 1935.

During the period 1916 to 1925, 1,072 patients were discharged. Of these, 457, or 42.6 per cent, were dead on discharge while 203, or 33 per cent, of the living cases had more than one discharge or were hospitalized for a period of less than ninety days. After these cases were subtracted, 87, or 21.1 per cent, of the remaining were not traced after discharge, leaving 325, or 30.3 per cent, of the original 1,072 individuals. The average length of hospitalization for the 325 cases traced was 1.1 years and the length of time followed after discharge was 7.8 years. A study of the mortality experience after discharge showed the ratio of actual to expected deaths to be 1.0 for the minimal, 5.4 for the moderately advanced and 19.9 for the far advanced.

The period from 1926 to 1935 shows a total of 2,922 patients discharged from the Sanatorium. Of this number 1,062, or 36.3 per cent, were dead on discharge while 554, or 29.8 per cent, of the remaining had more than one discharge or were hospitalized for less than ninety days. Ninety-three, or only 7.1 per cent, of the balance were not traced after discharge. Tables were presented of the remaining 1,213 cases showing such various characteristics on discharge as sex, age, classification of disease, condition, sputum examination, extrapulmonary tuberculosis and collapse therapy.

The average length of hospitalization for the 1,213 cases was 2.1 years and the average length of time followed after discharge was 4.5 years.

A study of the mortality risks shows that the minimal case of tuberculosis has his chance of dying during the first five years after discharge increased 1.4 times that of a person of the same age group in the general population. A higher risk appears in the advanced stages, the ratio of actual to expected deaths being 4.5 for the moderately advanced and 7.6 for the far advanced cases. When corrected for age differences these

ratios become 1.5 for the minimal, 4.0 for the moderately advanced and 7.4 for the far advanced.

Life-tables are compiled by age, stage of disease and condition on discharge. An inspection of the ratios of actual to expected deaths shows a better outlook for those who were arrested or apparently arrested on discharge than for those who were only quiescent, improved or unimproved.

A comparison is made of the individuals having a negative sputum with the entire group composed of both negative and positive sputum cases. Especially in those with far advanced tuberculosis the negative sputum cases seem to have a more favorable prognosis than the combined group.

Mortality statistics are also presented on patients with collapse therapy as opposed to those without this special form of treatment. The person-years of life experience are somewhat small in the moderately advanced group having pulmonary collapse, but in the far advanced group where the numbers are larger it would seem that, in the ages from twenty-five to fifty-four, cases with chest surgery experience a more favorable mortality than those without collapse treatment.

We wish to acknowledge our indebtedness to Dr. H. E. Hilleboe for his helpfulness in the preparation of this paper.

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MARITAL TUBERCULOSIS[1,2]

A Study of 210 Couples in Which Both Husband and Wife Have Clinical Tuberculosis

H. I. SPECTOR

The problem of marital tuberculosis is an important one, not only because of its social and public health aspects but also because it involves and challenges our conception of immunity and adult reinfection.

For the purpose of clarity the writer wishes to define marital tuberculosis as the development of clinical tuberculosis in both husband and wife. It is not assumed that transmission of the disease from the infected consort to the healthy one has taken place in each instance. Merely because the husband contracts clinical tuberculosis sometime after the wife developed the disease does not imply that the former contracted it from the latter. Clinical experience teaches us that it is possible for both husband and wife to contract the disease from either a son, daughter, grandmother or someone else. It is also possible for a tuberculous consort to marry a supposedly nontuberculous mate who at the time of marriage had an unrecognized latent or active tuberculosis. Due to these possible pit-falls, the fallacy of being dogmatic about infection from the tuberculous consort to the healthy one becomes obvious.

The following case histories of tuberculous families reported to the St. Louis Health Division shed some light on the difficulties encountered when one attempts to trace the source of infection from one member of the family to the others.

Undoubtedly infection from the tuberculous marital partner to the healthy one takes place in the majority of instances. However, absolute proof in this direction would require the examination of each couple, including tuberculin and roentgenographic studies before marriage and frequent follow-up studies after marriage not only of the married couples but also of their household contacts. This ideal approach is obviously impossible.

[1] Presented, in part, at the Joint Session of the Mississippi Valley Conference on Tuberculosis and the Mississippi Valley Sanatorium Association, St. Louis, Missouri, September 22, 1938.

[2] From the Tuberculosis Division of the St. Louis Health Department, St. Louis, Missouri.

FAMILY A			FAMILY B		
	Date reported as clinical tuberculosis to Health Division	Died		Date reported as clinical tuberculosis to Health Division	Died
Wife	9/ 9/27	9/20/27	Husband	2/23/28	
Son	12/19/32	4/19/33	Daughter	5/17/30	
Son	5/ 2/33	12/25/33	Wife	7/17/30	
Daughter	2/10/33		Niece	8/29/31	
Husband	5/ 1/35		Brother	10/ 1/31	
			Nephew	11/ 5/31	

FAMILY C			FAMILY D		
	Date reported as clinical tuberculosis to Health Division	Died		Date reported as clinical tuberculosis to Health Division	Died
Husband	4/14/31	9/10/31	Wife	6/29/20	2/ 5/21
Daughter	10/26/31		Sister	6/16/23	7/8/23
Daughter	10/ 8/32		Sister	1/20/24	1/3/26
Wife	10/31/32		Brother	3/31/24	
			Husband	12/ 1/32	

The importance of determining the possibility and frequency of marital infection, that is, infection from the tuberculous consort to the healthy one, and subsequent clinical disease should be clear to everyone. For if we contend that such infection is rare, it follows that marital tuberculosis is also rare and that immunity obtained during the childhood infection is generally lasting. In line with this reasoning, we should not hesitate to approve a contemplated marriage between a tuberculous individual with arrested disease and one who is free from the disease. On the other hand, if we believe in the transmission of the disease from the tuberculous wife or husband to the healthy consort, who had received his initial infection in childhood, we indirectly deny that lasting immunity exists. To be consistent we should accept the theory of exogenous reinfection in adults and should safeguard the consort's health by advising precaution against infection from the tuberculous mate.

A review of the literature regarding marital tuberculosis reveals contradictory reports in regard to many phases of the problem but especially in regard to frequency. On the one hand, Pope and Pearson (1) and the late Fishberg (2) present evidence that marital tuberculosis is extremely rare; on the other hand, Ward (3), Barnes (4), Minnig (5) and Opie and McPhedran (6) report studies proving that marital tuberculosis is frequent.

The figures as seen in table 1 are generally representative of these varying viewpoints.

The more recent literature on the subject, however, seems to concur with the view that marital tuberculosis is much more common than in the general population; Opie and McPhedran (6), for instance, in a recent study conclude that husbands and wives in marital contact with tuber-

TABLE 1

Frequency of marital tuberculosis as found in selected studies in various countries

	per cent
England	
Ward (3)	58.0
Weber (7)	14.7
France	
Delille (8)	11.0
Guerrin (9)	8 to 10
Germany	
Weinberg (10)	5.9
Samson (11)	32.6
Bieman (12)	4.3
Italy	
Bocchetti (13)	10.0
United States	
Fishberg (2)	2.9
Minnig (5)	16.8
Barnes (4)	40.0
Haywood, Morris and Wilson (14)	6.0
Opie and McPhedran (6) (figures on manifest tuberculosis only)	
In wives exposed to positive-sputum husbands	12.4
In wives exposed to negative-sputum husbands	4.5
In husbands exposed to positive-sputum wives	12.9
In husbands exposed to negative-sputum wives	8.3

culous disease, under varying conditions, are infected from five to nine times as often as persons with no known contact with the disease.

In order to gather wide-spread information, the writer recently sent a questionnaire covering not only subjects relating to the frequency of marital tuberculosis, but also points regarding the social aspect of the disease, to a selected group of phthisiologists in this and in certain European and South American countries.

Three hundred and three questionnaires were sent to 263 physicians in the United States and 40 to European and South American countries; 208 questionnaires were returned to the writer, 26 of which were from physicians of the following countries: England, France, Germany,

TABLE 2

Marital tuberculosis—tabulated figures on marital tuberculosis based on replies to questionnaires sent to 303 selected physicians in the United States and foreign countries—replies received from 208 or 68.6 per cent

QUESTION	YES	PER CENT	QUALIFIED YES	PER CENT	TOTAL PER CENT YES	NO	PER CENT	NO ANSWER OR DOUBTFUL	PER CENT
1. In your experience is marital tuberculosis a frequent occurrence?	56	26.9	7	3.4	30.3	122	58.7	23	11.0
2. Do you believe that the incidence of clinical tuberculosis is greater in the healthy consort of either the tuberculous husband or tuberculous wife than in the general population?	109	52.4	6	2.9	55.3	66	31.7	27	13.0
3. Do you believe that the chances for the development of clinical disease is greater in the husband of a tuberculous wife or in the wife of a tuberculous husband than in the children?	22	10.6	11	5.3	15.9	151	72.6	24	11.5
4. Do you approve of marriage (*a*) between tuberculous individuals with arrested disease?	131	63.0	41	19.7	82.7	23	11.0	13	6.3
(*b*) between a tuberculous individual with arrested disease and a nontuberculous one?	115	55.3	47	22.6	77.9	32	15.4	14	6.7
5. Do you believe that tuberculous married couples with arrested disease should ever have children?	103	49.5	51	24.5	74.0	38	18.3	16	7.7

Switzerland, Holland, Italy, Belgium, Algeria, Canada, Sweden, Czechoslovakia, Argentina and Spain. The results of the questionnaire are seen in table 2.

In analyzing table 2 it is interesting to note that the answers to certain

questions indicated a tendency to unanimity whereas answers to the other questions revealed considerable difference of opinion.

For instance, there was a divided opinion as to the frequency of marital tuberculosis, the majority believing that tuberculosis in both husband and wife is not common. At the same time a greater number of physicians believed that the incidence is greater than in the general population.

The answers further revealed that the greater number of physicians is inclined to permit marriage between arrested tuberculous individuals more often than between a tuberculous individual and a nontuberculous one. Most physicians (49.5 per cent) permit tuberculous couples to have children, whereas 24.5 per cent permit children only if the disease is not extensive, if it has remained arrested over a prolonged period of time, if the economic status warrants it and if the number of children is to be limited.

The question of marriage was the cause of many supplementary comments tending to emphasize that the danger of marriage is far greater to the wife when the husband is tuberculous than it is to the husband when the wife is tuberculous. Quite a number of physicians were of the opinion that marriage between arrested tuberculous individuals is safer than between a tuberculous and a nontuberculous individual, mainly because of a greater understanding and a sympathy for each other's physical limitations. Pattison (15) of Potts Memorial Hospital especially commented on this point.

The answers from the foreign countries, in the main, were very much like those of this country with the exception that the French physicians (16) stressed the importance of vaccinating the new born with BCG vaccine at birth, and that the German physicians (17) stated that marriage between a tuberculous individual and a nontuberculous one is prohibited by law in Germany.

From the information that has so far been presented, based, first, on the published statistical figures and, second, on the opinions of physicians obtained through the questionnaire, it is obvious that unanimity as to the frequency of marital tuberculosis as well as to the social phases of the subject is still lacking.

Since the studies as recorded in the literature are both unconvincing and contradictory and since the answers in the questionnaries are based merely on opinions in the majority of cases rather than on statistical facts, it was thought best to study the subject of marital tuberculosis from a different approach, namely, the statistical approach.

To begin with, it is significant to note that studies in regard to incidence in the past were based mainly on the histories obtained from tuberculous patients in dispensaries and sanatoria or their relatives rather than on actual clinical and epidemiological studies of tuberculous couples. In only a few instances were these studies supplemented by a physical and X-ray examination of the consorts.

A more serious criticism of the past methods of study lies in the failure on the part of the writers to compare the figures obtained in regard to the frequency of marital tuberculosis with the incidence rate of tuberculosis in the general population in the particular community where the study had been made. For we must admit that the incidence of tuberculosis in different countries and in different communities in each country is bound to vary. It seems apparent that failure to give the incidence rate of tuberculosis in the general population in the particular community where the study was made is an important omission and is mainly responsible for the statistical chaos that exists at the present time. The general tendency up till now, at least in this country, has been to assume that the incidence rate in the general population is about 1 per cent. It is important to realize that if we are to prove the frequency or rarity of clinical tuberculosis in married couples, and thus indirectly support or disprove the reinfection theory in adults, the statistical approach is the only sound method which will throw some light in this direction.

In this study an attempt is made to use the statistical method for interpreting the cases of marital tuberculosis. This approach is possible since we have figures on the number of reported cases and deaths for each year, and since we also know the marital status of each reported case. Figures are also available on tuberculosis in husband and wife for each year. The writer believes that a more accurate figure regarding the frequency of marital tuberculosis can be obtained by estimating the incidence rate of tuberculosis in both husband and wife in the reported married tuberculous and comparing same with the incidence rate in the general population.

It is true that not all tuberculous couples are known to us. It is likewise true that not all cases of tuberculosis in the community are known to us.

Our figures as to the number of couples with clinical active tuberculosis assume special importance from the viewpoint of accuracy of diagnosis if we take into consideration the fact that for years between 45 to 55 per cent of our tuberculous cases have been reported to us either a month

before death or after death. In other words, our study of marital tuberculosis is not based on a history of one marital partner or his relatives but on actual reported clinically active cases of tuberculosis in both husband and wife. In the majority of instances these couples were observed and diagnosed in our Municipal Chest Clinics. The living or dead cases of tuberculosis reported by the private physicians were investigated by the St. Louis Health Division's public health nurses. Many of the private physician's cases eventually came under the clinical supervision of the chest clinic staff of the St. Louis Health Division.

The study was based on 11,193 cases of tuberculosis reported during the ten-year period from 1928 to 1937 inclusive, 5,514 of which were

TABLE 3

Showing status of the 210 tuberculous couples

White	141	
Negro	69	
Total couples	210	or 420 persons
Second wives		2
		422 persons
Sputum		
Positive in both consorts in 43 couples or	86 persons	
Positive in husbands only	57 persons	
Positive in wives only	49 persons	
Total positive	192 persons	
Per cent positive		45.5
Questionable or negative in either		
Husband or wife	230 persons	
Per cent negative		54.5
	422 persons	or 100 per cent

married. From the latter group came the 210 couples who formed the basis upon which the study was made. Only tuberculous couples with clinical active disease, and not merely infected ones, were considered in this study.

The details as to the 210 tuberculous couples is seen in table 3.

The average period between the report of the first case and the report in the consort was for men, four years one month, for women, three years one month.

The number of reported cases and the incidence rate of marital tuberculosis are seen in tables 4 and 5, which are self-explanatory.

We were further interested in knowing whether the danger of infection

from the marital tuberculous partner is greater to the healthy consort or to the other contacts, especially to the children. For this purpose we studied the end results of the 210 couples by analyzing the case histories from the viewpoints of infection and the development of clinical disease

TABLE 4

Showing the incidence rate of tuberculosis in both husband and wife per 100,000 married tuberculous as compared with the tuberculosis rate in the general population, 1928 to 1937 inclusive

YEAR	ESTIMATED POPULATION	REPORTED CASES MARRIED AND SINGLE	RATE PER 100,000 IN GENERAL POPULATION	REPORTED CASES MARRIED	REPORTED TUBERCULOSIS IN BOTH HUSBAND AND WIFE	RATE OF MARITAL TUBERCULOSIS PER 100,000 MARRIED TUBERCULOUS
1928	813,586	1,587	195.0	766	15	1,958.2
1929	818,373	1,391	170.0	716	17	2,374.3
1930	823,157	1,216	147.7	582	24	4,123.7
1931	827,944	1,209	146.0	568	16	2,816.9
1932	832,731	1,152	138.3	561	19	3,386.8
1933	837,518	892	106.6	447	13	2,908.3
1934	842,305	989	117.4	491	27	5,499.0
1935	847,092	978	115.5	454	33	7,268.7
1936	851,879	895	105.1	492	26	5,284.6
1937	856,666	883	103.1	437	20	4,576.7
Total for ten years....	8,351,251	11,193		5,514	210	
Average per year.....	835,125	1,119.3	134	551.4	21	3,808.5

Incidence of tuberculosis in general population, based on ten-year average.....	.13 per cent
Incidence of tuberculosis in both husband and wife in married reported tuberculous.....	3.8 per cent

Risk of infection and development of clinical disease when in marital contact with an active case is 29 times as great as in general population.

Note: The author stated upon questioning that the increasing rate of marital tuberculosis is due to the long waiting list for sanatorium beds, the doubling up of many families due to the economic depression and the increased staff of the municipal nursing service, leading to a more complete check-up system, particularly in families in which a case of tuberculosis is known to exist. [Editor]

in contacts, and from the further viewpoint of mortality of both contacts and the tuberculous couples. Table 6 is self-explanatory.

The incidence rate of tuberculosis in contacts, 9 per cent or 69 times greater than in the general population, is much higher than found by Jean Downes (18), who reported the incidence rate to be at least 13 times greater than in the general population.

TABLE 5

Showing incidence rate of marital tuberculosis, as to color, per 100,000 married tuberculous

Reported Married Tuberculous

	WHITE	NEGRO	TOTAL
Male	1,995	983	2,978
Female	1,489	1,047	2,536
Total	3,484	2,030	5,514
Tuberculosis in couples	141	69	210
Rate per 100,000 married tuberculous	4,046.7	3,394.8	
Per cent	4.0	3.39	

TABLE 6

Showing end results in conjugal tuberculosis

Number of couples, 210:	
White, 141 or	282 persons
	2 second white wives
Negro, 69 or	138 persons
Total persons	422
Dead	
Husband and wife, 95 couples or	190 persons
Husbands alone	50 persons
Wives alone	41 persons
	281 or 66.58 per cent
Living	
Both husband and wife, 26 couples or	52 persons
Either husband or wife	89 persons
	141 persons
Number of couples whose contacts developed tuberculosis	37
Contacts	
Total number	595
Total number of contacts who developed tuberculosis	55 or 9 per cent
Dead	38 or 69 per cent
Incidence of tuberculosis in contacts of marital tuberculosis	9.0 per cent *
Incidence in general population	.13 per cent *

* A ratio of 69 to 1.

It is seen from table 6 that infection to contacts where marital tuberculosis exists is not only greater but more dangerous as indicated by the high mortality.

CONCLUSIONS

Conclusions based on this study are as follows:

1. Marital tuberculosis is not as infrequent as is generally believed.

2. While our statistics show that only 3.8 per cent of the reported cases of tuberculosis in married people are in both husband and wife, nevertheless, in St. Louis the risk of contracting the disease when in marital contact with an active case is 29 times greater than it is in the general population.

3. According to our figures the risk of contracting the disease for contacts exposed to marital tuberculosis is approximately 69 times greater than it is in the general population.

4. The evidence indirectly suggests that exogenous reinfection may be responsible for tuberculosis in the consorts.

5. The majority of physicians answering the questionnaire approve of marriage between tuberculous individuals and between a tuberculous and nontuberculous one.

6. The majority of phthisiologists permit their arrested married tuberculous to have children.

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OXYGEN TENSION AND THE TUBERCLE BACILLUS[1]

WALTER KEMPNER

The study of the energy supplying reactions of the tubercle bacillus under the physicochemical conditions occurring in tuberculosis may be of value in answering the question as to the mechanism by which the body spontaneously and under various forms of treatment combats the injurious action of tubercle bacilli. We are too accustomed to general explanations, such as, that the curative effect of high altitudes is due to the purity of air, radiated by a greater intensity of ultraviolet light; to the stimulating action of reduced oxygen pressure on the blood forming tissues "so that the blood is quickly regenerated after haemorrhage;" and to a rise in serum calcium (1, 2, 3). Or that the value of collapse therapy is due to the relaxation and resting of the lung, and to production of lymph stasis in the diseased part, "thus preventing spread of the disease and allowing nature to effect a cure" (4, 5). What we hear of the "defence reactions" of the body is mainly concerned with descriptive anatomy, that is to say, we are shown such states as tubercula, fibrosis or calcification without learning how these changes affect the organism which has caused them.

At least one experimental approach to this complex problem is afforded by the methods of cellular physiology. They enable us to obtain quantitative data on how anatomical cell conditions, as well as various forms of treatment, directly influence the vital chemical reactions of the tubercle bacillus, which may be assumed to be proportional to its injurious effects within the body. Both the defence reactions of the patient, and the therapies mentioned above, have in common the lowering of the oxygen tension in the tissue involved. This is obvious for high altitudes as well as for conditions of artificial pneumothorax, phrenic paralysis and thoracoplasty. Quantitatively it has been proved for areas of experimentally produced sterile inflammation, where the metabolism of the leucocytes leads to a decrease of oxygen tension dependent upon the amount of white blood cells present and the duration of the inflammation period (6).

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The lowest figure found in this series of experiments was an oxygen tension (oxygen partial pressure) of 6 mm. Hg, corresponding to an oxygen concentration of 0.8 vol. per cent of one atmosphere.

But the question that must be answered is: does this condition of lowered oxygen tension affect the tubercle bacillus, and in what way? Nearly all investigators (7, 8, 9, 10, 11) agree that the tubercle bacillus belongs to the strictly aerobic bacteria; when inoculating liquid culture media the pellicles are preferably placed in the upper layers, and, if the cultures (12) are kept in complete absence of oxygen at body temperature for three weeks, they perish, unable to obtain their life-sustaining energy by anaerobic fermentative splitting. Loebel, Shorr and Richardson (13) have shown that, through splitting of sugar to lactic acid anaerobically, the tubercle bacillus can obtain only one four hundredth of the energy gained by oxidation of sugar in air. This finding, in the view of the authors, explains the effect of tubercula and, according to Goldberg (14), the effect of collapse therapy on the bacillus. But though there may be complete absence of oxygen within a calcified tubercle, we are not justified in assuming this to be true for the lung tissue in high altitudes and in artificial pneumothorax (15). The *amount* of oxygen required by the bacillus probably will always be available under these conditions; the main difference is in the oxygen *tension*.

Webb, Boissevain and Ryder (8) examined the influence of oxygen and carbon dioxide on the growth of the human tubercle bacillus. They found that tubercle bacilli require an atmosphere containing a fairly high percentage of oxygen in order to grow, oxygen being the only gas required in appreciable amounts. No growth was observed (in 2 per cent glycerol broth) at 4 vol. per cent oxygen, and at 8 vol. per cent oxygen growth still was doubtful. Novy and Soule (9) examined glycerol agar cultures of tubercle bacilli inoculated by means of a spatula. The tubes were loosely plugged and placed in jars of 2 to 20 liters capacity containing the same amounts but different concentrations of oxygen. The oxygen consumption of the growing cultures was measured by determining the oxygen concentrations in the jars after a period of growth of twenty-eight to forty-two days. After twenty-eight days gas analysis of four jars with initial oxygen concentrations of 5.3, 2.9, 1.0 and 0.5 vol. per cent showed oxygen concentrations of 0.43, 0.41, 0.21 and 0.36 vol. per cent respectively; after forty-two days the oxygen concentration was zero in all the jars. Optimal growth was seen at 40 to 50 vol. per cent, but growth continued "until the last atom of oxygen was consumed."

The influence of oxygen tension on the respiration of cell suspensions containing equal amounts of cells which did not grow during the time of the experiment was quantitatively determined for the first time by Warburg (16, 17). By direct measurements he examined the oxygen consumption of phosphate suspensions of *Micrococcus candicans*, for example, at temperatures of 1° to 10°C. The manometer vessels were rotated at high speed to assure optimal gas diffusion to the surface of each single coccus. The same rate of oxygen consumption was found at an oxygen tension as low as 10^{-5} atmosphere (oxygen concentration of 0.001 vol. per cent) as in air. Since the publication of Warburg's experiments it has been considered an established fact that the ***respiration of bacteria and body cells is independent of variations of oxygen tension, cell respiration remaining unchanged as long as the smallest amount of oxygen is left.*** Opposite results which seemed to indicate a dependence of cell respiration on oxygen tension were criticized (16, 17, 18, 19) as being vitiated by the technical error of insufficient oxygen diffusion. Even at last year's meeting of the American Physiological Society, in a special symposium on anoxia, it was again emphasized (R. W. Gerard) that oxygen tension as such could in no way be considered as a limiting factor of cellular respiration.

We have, however, examined numerous body cells and bacteria at low oxygen tensions by methods which exclude the possibility of insufficient gas diffusion (20, 21, 22) and found that, contrary to the "all or nothing theory of cellular respiration," there is a considerable effect of oxygen tension on respiration. But this effect is influenced by changes of the milieu (salt content, carbon dioxide concentration, temperature) to such an extent that the whole phenomenon easily could be overlooked under unfavorable experimental conditions. At body temperature and in a physiological milieu the respiration of all normal uninjured young animal cells and bacteria examined proved to be very markedly inhibited by low oxygen tension. The respiration of *Micrococcus candicans* for example, which at 12°C. was the same at an oxygen tension lowered to 15 mm. Hg as in air, at 37°C. was inhibited by 60 per cent. Since this effect of oxygen tension, though quantitatively varying with the type of cell, was found in cells differing as widely in type as nucleated red blood cells of fowl and cold-blooded animals, human erythroblasts and leukaemic blood cells, kidney slices, pneumococcus, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas pyocyanea*, *Monilia albicans* and young plant cells, it might seem justifiable to draw a general conclusion

on all cellular respiration. But the tubercle bacillus is exceptional in many respects; its respiration is independent of pH changes within such wide limits as between 1.5 and 12 (13, 23). One could therefore not simply assume its sensitivity to variations of oxygen tension to be identical with that of cells previously examined.

This paper gives the results of experiments in which the respiration metabolism of the tubercle bacillus was measured manometrically with the Warburg technique at 14 different partial pressures of oxygen.

EXPERIMENTAL

Tubercle bacilli, H37,[2] cultivated on Steenken and Smith medium (24), were used. The cultures were fifteen to twenty days old. The bacteria were washed from the solid culture medium and suspended in m/50 phosphate (P_H 7.4)−m/80 glycerol solution. The dry weight was determined after centrifuging aliquot parts of the suspension fluid and drying at 100°C. (25). One cc. of suspension fluid contained 7 to 15 mg. bacteria.

Two cc. of the suspension fluid were pipetted into a conical Warburg manometer vessel of 18.5 cc. capacity. To absorb the carbon dioxide in the oxygen consumption experiment, the side bulb of the vessel contained 0.2 cc. of 10 per cent sodium hydroxide, which for the determination of the respiratory quotient was removed and replaced by 0.2 cc. m/20 lactic acid. The temperature of the water bath was 37.8°C. In order to assure optimal gas exchange between gas space and each cell under observation, the manometer vessel was shaken at a speed of 210 oscillations per minute. Controls showed that regardless of the oxygen tension employed, increase of the shaking speed did not alter the results, nor did decrease of the shaking speed to 90 oscillations per minute, at an oxygen tension as low as 2 vol. per cent, cause any change in the manometrical readings.

The manometer vessels with the suspensions were saturated with air and shaken in the thermostat for one hour. Then the respiration of the tubercle bacilli was measured in thirty-minute periods at definite oxygen tensions. The vessel was saturated with nitrogen-oxygen mixtures of different concentrations which were prepared over mercury in a gasometer of two and a half liters capacity. (See figure 1.) The manometer was not removed from the thermostat during the experiments and was

[2] My most cordial thanks are due to Dr. E. R. Baldwin, Trudeau Foundation, who kindly provided me with the cultures.

stopped for only ten seconds to open and to close the stop-cocks; otherwise the vessel was constantly shaken during the saturation (four minutes), as well as when the readings were made (every five minutes). After four constant readings a new gas mixture was passed through the vessel. During the whole time of the experiment the tubercle bacilli showed no growth and no diminution of their metabolic activity; the rate of oxygen consumption in air was exactly the same in the beginning and at the end of the experiment, even after experimental periods of twenty-four hours.

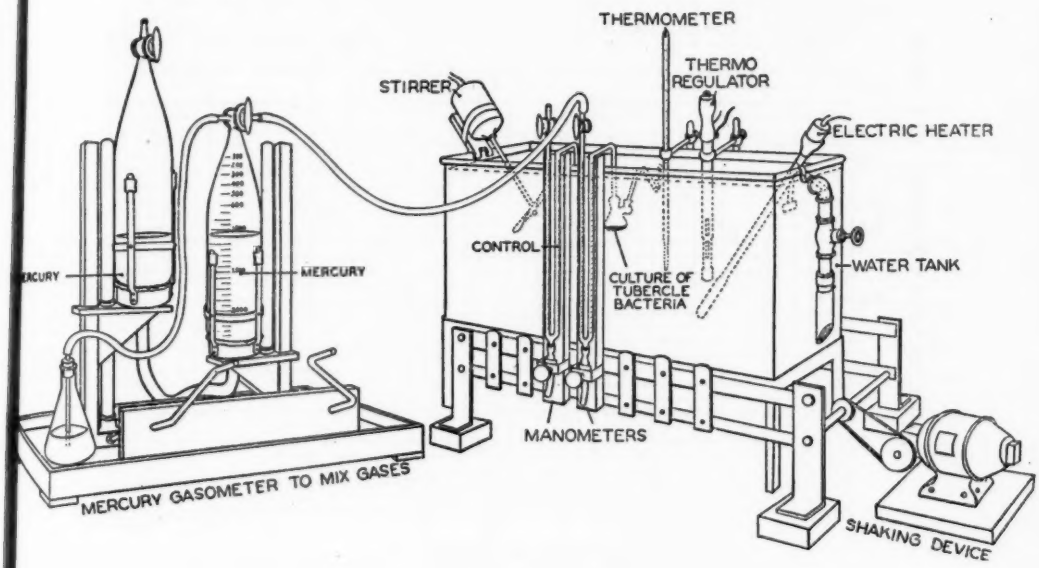

FIG. 1

Chart 1 shows the results of a typical experiment.

The rate of respiration of the tubercle bacilli reaches nearly its maximum at oxygen concentrations between 12 and 14 vol. per cent of one atmosphere (oxygen partial pressures between 91 and 106 mm. Hg). Further increase of the oxygen concentration, 20 to 100 vol. per cent (152 to 760 mm. Hg), produces only an increase of about 6 per cent. A definite inhibition, as compared with the rate of respiration in air, occurs, however, at an oxygen concentration as high as 8 vol. per cent (60.8 mm. Hg); the inhibition is 20.4 per cent. At 5 vol. per cent oxygen (38 mm. Hg) it is 28 per cent; at 2 vol. per cent (15.2 mm. Hg) 58 per cent; at

1.1 vol. per cent (8.4 mm. Hg) 70 per cent. This shows that the respiration of tubercle bacilli is highly dependent upon variations of oxygen con-

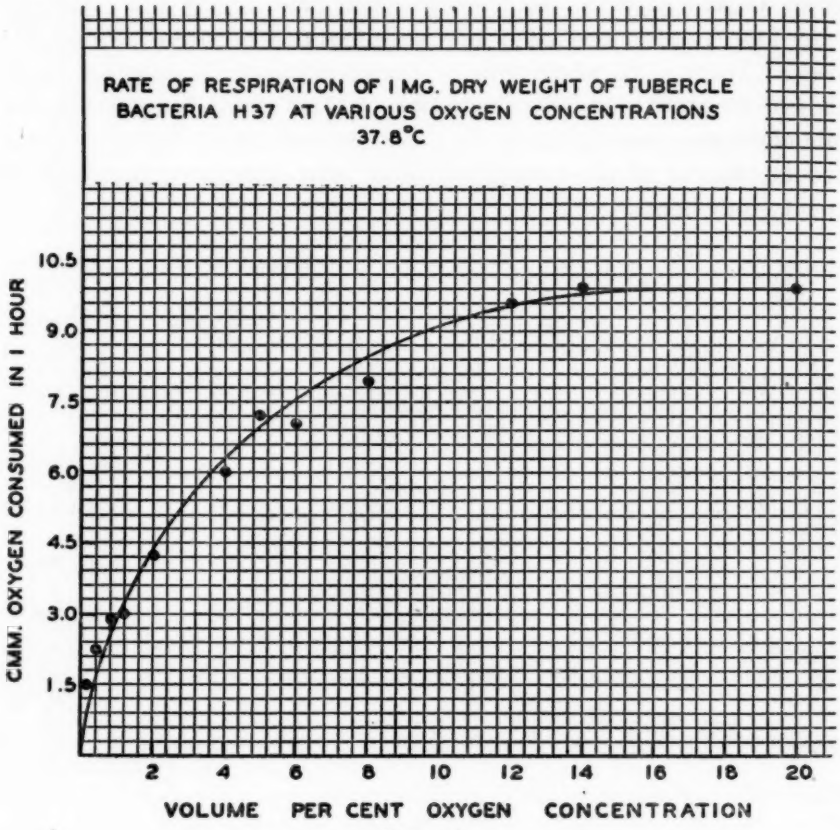

CHART 1

TABLE 1

Metabolism of 1 mg. (dry weight) of tubercle bacilli per hour at various oxygen tensions, at 37.8°C.

MM. Hg OXYGEN PARTIAL PRESSURE	CMM. OXYGEN CONSUMED	CMM. CARBON DIOXIDE FORMED	RESPIRATORY QUOTIENT	PER CENT INHIBITION OF RESPIRATION
760–160	10.02	7.52	0.75	0
45.6	7.04	5.42	0.77	29.7
8.7	2.98	2.18	0.73	70.3

centration (oxygen partial pressure) especially at those oxygen concentrations that actually occur in the body. The oxygen saturation curve of the oxygen transferring ferment of respiration in the tubercle bacillus

is very similar in shape to that found for pneumococcus (21) and to the dissociation curves of oxyhaemoglobin (26).

Contrary to the experiences with nucleated blood cells (20, 22), the respiratory quotient remains almost constant for all oxygen tensions examined, in spite of the marked decrease of the respiration rate with lowered oxygen tensions. Table 1 shows the respiratory quotient at various oxygen tensions.

DISCUSSION

The finding that the respiratory metabolism, the main source of energy of tubercle bacilli, is a direct function of oxygen tension, makes it possible to discuss, at least from one clearly defined viewpoint, the mechanism of the fight of nature and medical treatment against the bacillus. We purposely limit this discussion to the inferences that can be drawn from the quantitative data presented above, and shall not speak here of other forms of treatment of tuberculosis, such as dietary measures, tuberculin treatment, etc. As the experiments have shown, the chemical reactions, and therewith the injurious effects of tubercle bacilli, are inhibited by low oxygen tension. If, on the basis of this result, one analyzes the mechanism of high altitude treatment in pulmonary tuberculosis, for example, and substitutes the figures obtained on the inhibition of bacterial respiration by low atmospheric oxygen concentration for the usual "pure air" hypothesis, interpretations and conclusions present themselves that also may be of value for problems of practical therapeutics.

At sea level the oxygen tension of atmospheric air is about $0.21 \times 760 = 159.5$ mm. Hg and that of alveolar air 100 mm. Hg; at 10,000 ft. altitude the atmospheric oxygen tension is $0.21 \times 540 = 113$ mm. Hg, the oxygen tension of alveolar air is about 62 mm. Hg (26, 27). What this difference in alveolar oxygen tension means for the tuberculous process in the body cannot simply be read from the curve (chart 1) which shows that the respiration of tubercle bacilli at 62 mm. Hg is inhibited by 20.4 per cent compared to their respiration at 113 mm. Hg. The oxygen tension to which the tubercle bacilli are exposed in the lung cannot, in the majority of cases, be assumed to be equal to that of alveolar air but rather to that beyond the alveolar wall. We must, moreover, include in our calculations the important factor of the reaction of the tissue, producing a leucocytic barrier around the invading bacillus (6);

this causes a further considerable lowering of the oxygen tension, since human leucocytes possess a very high respiratory metabolism (table 2).

Direct quantitative determinations of the oxygen tension within a tubercle have not been possible. But it is evident that the final oxygen tension within the tubercle must change with the variations of the initial oxygen tension in the alveolus. If we assume that the oxygen consumption of the surrounding tissue and of the leucocytic barrier causes 1 cc. of tissue fluid to lose in a given time 1.5 cmm. oxygen on the way between alveolus and tubercle, then the oxygen content within the tubercle would be at sea level $24 \cdot \frac{100}{760} - 1.5 = 1.66$ cmm. oxygen per cc., corresponding to an oxygen tension of 52.4 mm. Hg. At an altitude of 10,000 ft., when the initial alveolar oxygen tension is 62 mm. Hg, the oxygen content within the tubercle, under the premise of an equal amount of oxygen lost on the way, would be $24 \cdot \frac{62}{760} - 1.5 = 0.46$ cmm. oxygen

TABLE 2

Respiration in air of 1 mg. dry weight of cells in one hour

TYPE OF CELLS	CMM. OXYGEN CONSUMED
Human exudate leucocytes:	
Mostly polynuclear cells (6)	22.8
Mostly lymphocytic cells (26)	10.4
Tubercle bacilli, H37	10.7

per cc., corresponding to an oxygen tension of 14.5 mm. Hg. If we take into consideration the lower leucocyte (20) and tissue respiration rate probable at lower oxygen tensions, and hence assume the amount of oxygen lost on the way between alveolus and tubercle to be only two-thirds of that lost at higher oxygen tension, the oxygen content within the tubercle would be $24 \cdot \frac{62}{760} - 1.5 \cdot \frac{2}{3} = 0.96$ cmm. oxygen per cc., corresponding to an oxygen tension of 33.2 mm. Hg.

These calculations show that when the tuberculous process is going on behind the alveolar wall and a layer of leucocytes, the actual oxygen tension to which the tubercle bacilli are exposed would be at sea level 52 mm. Hg and at 10,000 ft. altitude between 33.2 and 14.5 mm. Hg. As seen in the curve, this difference in oxygen tension is followed by a very marked change in the rate of the energy yielding reactions of

tubercle bacilli. Assuming the cellular defence conditions to remain constant, the inhibition of the bacterial respiration would be only 20 per cent at sea level, but from 33 to 58 per cent at 10,000 ft. altitude.

The factor of the oxygen concentration in the air breathed, and accordingly of the initial oxygen tension in the alveolus, becomes increasingly important the more the defence reactions of the body, that is, the accumulation of white blood cells and the formation of fibrous tissue, have increased the amount of oxygen lost between the alveolus and the actual site of the bacillus. This is true especially for that region of the curve where a very steep drop in the bacterial metabolic reactions is seen.

On the other hand it is obvious that when the tuberculous lesion is in an area that always has a maximal supply of oxygen in concentrations above the level critical for tubercle bacilli, and when the body itself fails to produce any of the defence reactions that cause oxygen loss and lower the oxygen tension, low oxygen therapy alone will not be sufficient to inhibit the activity of the tubercle bacillus to any appreciable degree. It is also obvious that there is no reason for a treatment by means of which the alveolar oxygen tension is lowered when the defence reactions of the body have already produced a milieu in which the bacteria are asphyxiated by complete anaerobiosis, as in calcification. These are the two extremes where, from the point of view of the biology of the tubercle bacillus, low oxygen tension therapy becomes ineffective.

The same line of reasoning as in the instance of high altitude treatment can be employed for other forms of low oxygen tension treatment in pulmonary tuberculosis: for pneumothorax, thoracoplasty, phrenic paralysis, etc. It has to be modified for tuberculous lesions of other organs and of those areas of the lungs not lying in the immediate vicinity of the alveoli, in such a way that the oxygen tension of the blood and tissue fluid in between receives special consideration. Here one generally meets with the objection that lowering of the oxygen tension in the alveolar air does not influence the oxygen tension in the healthy or diseased organs, since the oxygen saturation of haemoglobin, with a decrease of oxygen tension from 100 to 62 mm. Hg for example, only decreases from 94 per cent to 86 per cent (26), and a marked drop does not occur until a much lower oxygen tension is reached. This objection is neither in agreement with the experimental results of Campbell (28, 29), who showed that the decrease of oxygen tension in the air breathed markedly decreases the oxygen tension in the tissues, nor does it consider the simple experience that, in spite of the well maintained oxygen saturation of

haemoglobin, the body reacts to high altitudes with such striking manifestations as mountain sickness and increased formation of red blood cells.

Likewise the argument fails to take into account the fact that the rate of metabolism of tubercle bacilli, as that of other bacteria and body cells, is not determined by the *amount* of oxygen available but by the actual oxygen *concentration*. The process follows the same pattern as in lactic acid formation by leucocytes, the rate of which depends on the sugar concentration in the suspension medium. The lactic acid formation drops to minimal values when fermentation takes place in 10 cc. of a 10 mg. per cent sugar solution instead of in 1 cc. of a 100 mg. per cent solution, although the absolute amount of sugar available to the leucocytes remains the same (30). Equally the oxidative metabolism of tubercle bacilli drops to minimal values when the oxygen concentration decreases from 10 vol. per cent to 1 vol. per cent, although the amount of oxygen available is kept constant. Regardless of the *amount* of oxygen carried by the haemoglobin in a given time, the maximum of the oxygen *tension* of the blood is always determined by the oxygen tension of the alveolar air.

The oxygen tension of the blood, on the other hand, determines the maximum oxygen tension of the tissue fluid with which the bacteria are in intimate contact at the site of the tuberculous lesion. Since oxygen is lost in the blood on the way from alveolus to capillary, as well as in the tissues before reaching the tubercle bacillus, it follows according to the calculations used above that the oxygen concentration around the tubercle bacillus will be correspondingly lower the lower the oxygen tension of the atmosphere, or of the alveolar air, or of the blood at the outset. As demonstrated for pulmonary tuberculosis, in the tuberculosis of other organs also, the treatment with low oxygen tension will not produce the decisive therapeutic effect of inhibiting the bacterial metabolism unless the local cellular reactions contribute to further decreasing the oxygen tension to such a degree that the bacillus is deprived of most of its energy supply, and thus is rendered harmless.

How low oxygen therapy influences the general condition of the patient and pathological manifestations secondary to the tuberculous process is not within the scope of this discussion, which is only concerned with the direct effect of the therapy on the tubercle bacillus itself. In this connection, however, it may be mentioned that high oxygen tension treatment, though it may afford symptomatic relief in many instances

of circulatory insufficiency secondary to the bacterial affection, raises the oxygen tension in the tissues (28, 29) and should therefore be applied unhesitatingly only in the two clinical types referred to above: first, where every form of causal therapy has to be abandoned, and second, where the body, by segregating the process, has by its own resources already overcome the disease, and the patient suffers from residual symptoms. In all other cases it must be remembered that high oxygen tension produces conditions most favorable for the metabolism of the tubercle bacillus and counteracts the efforts of the body to overcome the disease by inhibiting the bacterial reactions.

SUMMARY

The respiratory metabolism of fifteen to twenty day old cultures of the tubercle bacillus H37 was measured manometrically by the Warburg methods in m/80 glycerol-m/50 phosphate (P_H 7.4) at 14 different oxygen concentrations between 0.1 and 100 per cent of one atmosphere (oxygen partial pressures of 0.76 and 760 mm. Hg).

Contrary to the "all or nothing theory" of cellular respiration, the respiration of tubercle bacilli was found to be highly dependent on variations of oxygen concentration, especially at those concentrations that actually occur in the body. At 8 vol. per cent oxygen concentration the respiration was inhibited by 20.4 per cent, at 2 vol. per cent by 58 per cent, at 1.1 vol. per cent by 70 per cent. The oxygen saturation curve of the oxygen transferring ferment of respiration in the tubercle bacillus is very similar in shape to that found for pneumococcus and to the dissociation curves of oxyhaemoglobin. The respiratory quotient of the tubercle bacillus remained constant for all oxygen tensions applied.

Since the oxidative metabolism is practically the only source of energy for the tubercle bacillus, the direct inhibitory influence of low oxygen concentration on its respiration will cause "starvation," impairment of the chemical reactions and therefore a decrease of the injurious effects of the bacillus. The beneficial effect of various forms of treatment (high altitude, pneumothorax, phrenic paralysis, thoracoplasty) is discussed on the basis of this finding.

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CROTONALDEHYDE IN EXPERIMENTAL TUBERCULOSIS[1]

ROBERT L. INGERSOLL, MILDRED WINN AND CARL C. LINDEGREN

Vollrath, Walton and Lindegren (5) showed that crotonaldehyde and acrolein vapors are bactericidal. The following experiments were performed to test their value in experimental tuberculosis.

Experiment 1: Twelve guinea pigs were inoculated intratracheally with sputum from a tuberculous patient. Twenty-four hours later the guinea pigs were placed in two cages, each containing 6 animals. The animals in one cage were given drinking water containing 1:1,000 acrolein, the animals in the other cage served as controls.

On the average, the treated animals survived somewhat longer than the controls. Although this advantage was not significant, it seemed sufficient to warrant further work.

Subsequent *in vitro* experiments (Ingersoll, Vollrath, Scott and Lindegren (2)) on the comparative bactericidal value of acrolein and crotonaldehyde showed that crotonaldehyde is possibly a better therapeutic agent, so in all following experiments it was used.

Experiment 2: Sixteen guinea pigs were inoculated intratracheally with sputum obtained from open cases of pulmonary tuberculosis. Eight animals were exposed for two hours daily to the vapors from a solution of crotonaldehyde. A continuous flow of air was allowed to bubble slowly through a 1:4,000 aqueous solution of crotonaldehyde, half-filling a 10-gallon carboy. The resultant vapors were released into a small chamber which held the 8 treated animals.

In this case, also, the treated animals seemed to do better than the controls. Five additional, uninoculated animals survived daily treatment with the vapors and, when killed and autopsied at the end of the experiment, appeared to be healthy, showing no apparent injury resulting from the vapors.

Experiment 3: Twelve mg. of three different strains of pure cultures of tubercle bacilli were dried, weighed and suspended in 7 cc. of a 1:10,000 solution of sodium carbonate (Calmette (1)). Each of 49 animals was inoculated intratracheally with 0.1 cc. of the suspension. Forty hours after inoculation, treatment was begun.

[1] From the University of Southern California, Los Angeles, California.

Twenty-five animals were exposed to the vapors of a 1:8,000 aqueous solution of crotonaldehyde for eight hours daily over a period of fifty-five days. Twenty-three control animals received no treatment.

The amount of tuberculosis present was designated as 0, +, ++, +++, ++++, according to the scheme devised by Petroff, Branch and Jennings (4). Briefly, it is as follows:

0 = no visible evidence of tuberculosis

\+ = tubercles at local site of inoculation, with or without lymph node involvement; a few isolated tubercles may be found in lung and spleen

++ = tubercles in two or three of the organs usually involved, such as lung, liver, spleen and lymph nodes

+++ = generalized tuberculosis not of the fulminating type (see ++++). In this category also are included animals with extensive active lesions in one or more organs.

++++ = fulminating generalized tuberculosis, that is, enlarged spleen, with infarcts, infarcts in the liver, multiple tubercles in the lungs, and involvement of the lymph nodes. Ruptured spleen and allergic phenomena, such as fluid in the pleural and peritoneal cavities, not uncommon in this group.

On the twenty-fifth day a treated animal died, probably of pneumonia, since the amount of tuberculosis (+) was less than that usually necessary to cause death. Thirteen other treated animals died later from a similar infection.

The small chamber in which the treated animals were confined during the warmest eight hours of the day had a maximal humidity. This was due to the vaporizing of the water containing the crotonaldehyde, and to the high temperature produced by heat generated by the animals themselves. When they were transferred for the night to a large, unheated room containing the control animals, their fur was damp and they were overheated. This change from a warm damp box to a cold room explains the development of pneumonia in the treated guinea pigs, and its comparative absence in the controls, not subjected to the same conditions.

Microscopical and cultural analysis revealed no tubercle bacilli in any of the animals designated as having a 0 degree of gross tuberculosis, thus eliminating the possibility that the pneumonia was due to a septicaemic tuberculosis. Tubercle bacilli were found in the tissues of all animals having ++ or more tuberculosis.

Due to the deaths from pneumonia in the treated animals it was de-

cided to kill all the remaining animals, and this was completed on the fifty-fifth day. Table 1 shows that the extent of gross tuberculosis in the control animals far exceeds that in the treated. It seems to be the general opinion that pneumonia would hasten rather than retard the development of the tuberculous lesions.

TABLE 1

Autopsy findings on animals used in experiment 3

EXTENT OF GROSS TUBERCULOSIS	TREATED	CONTROL
0	19*	0
+	6	1
++	0	10
+++	0	10
++++	0	2

* Microscopical and cultural analysis revealed no tubercle bacilli in any of animals with 0 degree of tuberculosis.

Thirteen of the treated animals died between the 25th and the 40th day; all others (treated and control) were sacrificed between the 36th and the 55th day.

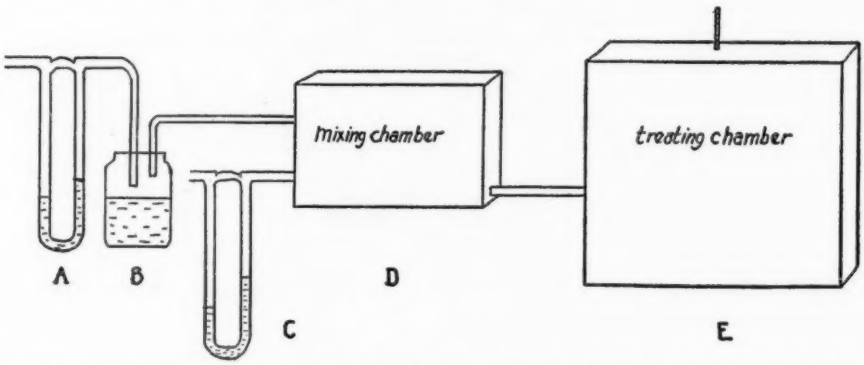

FIG. 1. Diagram of the apparatus used in experiment 4. A and C are flowmeters, B is the bottle containing pure crotonaldehyde, D is the mixing chamber, and E is the treating chamber.

Experiment 4: The next experiment was designed to avoid the complication brought about by the high humidity in the treating chamber. Figure 1 shows the diagram of the apparatus patterned after that designed by Patty, Schrenk and Yant (3). Compressed air, passing through flowmeter A, was blown over the surface of crotonaldehyde in container B and passed into mixing chamber D. Simultaneously, compressed air passing through flowmeter C was passed into the mixing

chamber to dilute the crotonaldehyde vapors. Maintenance of the levels of the two flowmeters made it possible to standardize the amount of crotonaldehyde in the treating chamber E. This amount was sufficient to kill a weak suspension of *Mycobacterium smegmatis*, spread on the surface of an agar plate, in one hour.

The treating chamber was composed of two 100-gallon steel barrels welded together. The temperature in the chamber was kept around 25°C.

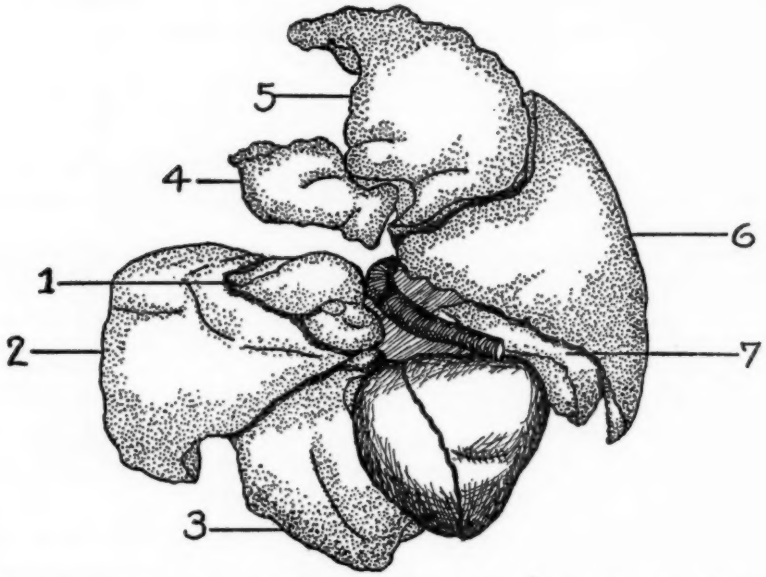

FIG. 2. Heart and lungs of the guinea pig, ventral view, showing the scheme followed in numbering the different segments of the lungs.

Sixty-five guinea pigs were inoculated with a culture of *Mycobacterium tuberculosis*, which had been cultured on Herrold's medium from guinea pigs inoculated with sputum of tuberculous patients. One-tenth cc. of a heavy suspension of bacteria in 1:10,000 sodium carbonate was injected into the exposed trachea of each animal, under light ether anaesthesia.

After the intratracheal inoculation the guinea pigs were divided into two groups of 33 and 32 animals. One of these groups was exposed for four hours daily to the crotonaldehyde vapors. The second group served as a control, being subjected to a constant flow of untreated air in the chambers for four hours each day. Sixteen uninoculated animals

served as further controls on the effect of the crotonaldehyde. These were divided into two groups of 8 animals each, one group receiving treatment of crotonaldehyde vapors, the other being subjected to untreated air. They were kept in the same cages with the inoculated animals.

On the twenty-sixth day all animals were killed. They were suspended head down, the jugular vein cut, and allowed to bleed to death. After autopsy, the internal organs were preserved in Kaiserling's solution.

TABLE 2

Total number of tubercles in lung sections of animals used in experiment 4

TOTAL NUMBER OF TUBERCLES PER ANIMAL	TREATED	CONTROL
0– 20	11	8
21– 40	8	5
41– 60	8	7
61– 80	4	4
81–100	1	5
101–120	1	1
121–140	0	2

TABLE 3

Frequency distribution of external tubercles of different diameters (experiment 4)

CLASS RANGE IN 1/60-INCH UNITS	TREATED	CONTROL
	per cent	*per cent*
1– 4	53.9	39.5
5– 8	39.9	47.3
9–12	5.8	11.0
13–16	0.4	1.9
17–20	0.0	0.3
Number of tubercles measured.....	740	919

According to Petroff's scheme, all the animals were found to be in classes 0 and +. Therefore, the tubercles were measured and counted to make a finer distinction. The different segments of the lungs were numbered, according to the scheme followed in figure 2. The external tubercles on each segment were counted and their diameters measured. Then the several segments (with the exception of number 1) were split to expose as large an internal surface as possible. The number of tubercles exposed on the cut surfaces, plus the number of external

tubercles is shown in table 2. These figures do not represent the grand total of tubercles in each animal for many tubercles were not exposed by the single cut through each segment. The average number of tubercles in the control animals was 51.4 and that of the treated was 40.3.

Table 3 shows a comparison of the diameters of the external tubercles in the control and treated animals. The average diameter of the external tubercles of the control animals (in sixtieths of an inch) was 5.61; the average diameter of those of the treated animals was 4.73. The ratio of the volume of tubercles in the control animals to the volume of tubercles in the treated animals is given by the formula:

$$\frac{(\text{average diameter of control tubercles})^3 \times \text{average number control tubercles}}{(\text{average diameter of treated tubercles})^3 \times \text{average number treated tubercles}}$$

$$= \frac{(5.61)^3 \times 51.4}{(4.73)^3 \times 40.3} = 2.13.$$

SUMMARY

Experiments on guinea pigs artificially inoculated with tuberculosis seem to indicate that fewer and smaller tubercles develop in animals treated with crotonaldehyde than in untreated control animals.

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COEXISTING TUBERCULOSIS AND SYPHILIS[1,2,3]

FREDERICK C. WARRING, JR.

The earlier reports in the literature on the problems encountered in patients with coexisting tuberculosis and syphilis, especially from the viewpoint of treatment, are summarized by Potter (1). An excellent critical review of the subject by Padgett and Moore (2) contains a bibliography of more recent articles and compares differences of opinion on the various questions. Since then Smith (3) has presented his findings on the treatment of syphilis in 68 patients with pulmonary tuberculosis.

From January 1, 1928 to January 1, 1938, routine serological tests for syphilis were performed on 2,160 patients admitted to the Laurel Heights State Tuberculosis Sanatorium. This is a study of the interrelations of tuberculosis, syphilis and antisyphilitic treatment in those patients in this group who were found to have the two diseases. The material at hand has been carefully compiled and analyzed in the light of these problems:

1: The incidence of syphilis in patients admitted to the Sanatorium
2: The classification of the syphilitic infections
3: Behavior of tuberculosis in the presence of syphilis
4: Behavior of syphilis in the presence of tuberculosis
5: Indications for, and influence of, antisyphilitic treatment
6: Syphilis of the lung

The statistical evidence is presented simply and is not analyzed by modern statistical methods.

All of the patients, syphilitic and nonsyphilitic, were treated according to the modern concept of the management of pulmonary tuberculosis, that is, by bed-rest, supplemented, when indicated, with surgery performed at the Sanatorium. Diagnosis of tuberculosis was made by sputum examination or roentgenogram or both and the progress of the

[1] From Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

[2] Read before a meeting of the Connecticut State Tuberculosis Physicians, January 9, 1939.

[3] Dr. Allan K. Poole, Associate Professor of Clinical Medicine of the Yale School of Medicine, has very kindly criticized the material so that the study represents the coöperative efforts of the tuberculosis physician and the syphilologist.

disease was followed by frequent stereoscopic X-ray films, laboratory and clinical findings. The classification of the tuberculosis and the condition of the patient at discharge as given are in accord with the Standards of the National Tuberculosis Association.

Anamnesis, physical examination and serological studies, with spinal fluid examinations when possible, were the basis of the diagnosis and classification of the cases of syphilis. The Wassermann reaction and Kahn test were employed during the first nine and one-half years of the study. During the last six months the Kline diagnostic test was used, checking doubtful or positive reactors with subsequent Wassermann reactions or flocculation tests.

TABLE 1

Incidence of syphilis in patients admitted to the Laurel Heights Sanatorium

	PATIENTS TESTED	POSITIVE OR DOUBTFUL SEROLOGY	DIAGNOSIS MADE OF SYPHILIS
Total admissions	2,160	106 (4.9%)	87 (4.0%)
White male	1,240	60 (4.8%)	48 (3.9%)
White female	843	24 (2.8%)	19 (2.3%)
Total white	2,083	84 (4.0%)	67 (3.2%)
Colored male	48	11 (22.9%)	9 (18.7%)
Colored female	29	11 (38.0%)	11 (38.0%)
Total colored	77	22 (28.6%)	20 (26.0%)

THE INCIDENCE OF SYPHILIS IN PATIENTS ADMITTED TO THE SANATORIUM

The incidence of syphilis in admissions is shown in table 1.

Table 2 gives the analysis of the 22 admissions showing positive or doubtful reactions that could not be given a final diagnosis of syphilis. We are especially interested in the 11 repeatedly doubtful reactors. These constitute 10 per cent of the total reactors and it is felt that this is a larger proportion than is generally found in the syphilis clinics. This brings up the question of false-doubtful or positive reactions for syphilis obtained in tuberculous patients.

Parran and Emerson (4) sent blood from 458 supposedly nonsyphilitic tuberculous patients to five outstanding serologists. They found both typical and atypical false-doubtful and false-positive results in these sera and felt that tuberculous toxaemia might contribute a confusing factor to syphilis serology.

CLASSIFICATION OF SYPHILITIC INFECTIONS

As to the patients definitely diagnosed, their classification is presented in table 3. Patients do not primarily come to sanatoria for diagnosis and treatment of their syphilis and as a result of this artificial selection it is to be expected that the late types of the disease predominate in our admissions. There are no primary or secondary lesions in this series.

TABLE 2

Cases with doubtful, or a single positive, complement fixation or flocculation tests on whom a positive diagnosis of syphilis could not be made

Doubtful reactions, repeated	11
Doubtful reactions, not repeated	3
Single positive, repeated negative	5
Single doubtful, repeated negative	3
	22

TABLE 3

Classification of cases of syphilis on admission

Late congenital	1
Latent	68
Aortitis	3
Aneurysm	2
Aortitis, osteitis, skin gumma	1
Skin gumma	1
Hepatitis (?)	1
Central nervous system syphilis:	
8th nerve	1
Tabes	1
Unclassified	4
Biological cure (?)	1
History—treated—serological cure	3
	87

The latent group cannot be accurately divided into early and late stages, but the majority of them are probably in the late latent stage.

IS THE BEHAVIOR OF PULMONARY TUBERCULOSIS MODIFIED BY THE PRESENCE OF SYPHILIS?

Three stages of the behavior of pulmonary tuberculosis in a syphilitic patient can be studied and compared with the course of the disease in nonsyphilitics.

(a) *Incidence of development of active tuberculosis:* We have no statis-

tics of our own to present on this question. Statistical evidence on this point comes from general hospitals and clinics where large numbers of syphilitic patients are seen. There appears to be a lesser incidence of development of active tuberculosis in syphilitics than in nonsyphilitics. Landsberger (5) found that, in 5,323 cases at autopsy, 10.1 per cent of the syphilitic patients and 24.9 per cent of the nonsyphilitics showed evidence of active tuberculous lesions. Turner (6) studied 10,000 admissions to the syphilis clinic of the Johns Hopkins Hospital and found that 1.6 per cent of the Negroes also had clinically active pulmonary tuberculosis, while the incidence in the Negro population from which group the clinic patients came was 2.6 per cent. Padgett and Moore (2) in 6,000 consecutive admissions to the medical wards of the same

TABLE 4

Classification of tuberculosis on admission

	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED
White:			
Syphilitic	6.6% (4)	31.2% (19)	62.2% (38)
Nonsyphilitic	8.4% (159)	28.2% (538)	63.4% (1,208)
Colored:			
Syphilitic	0	31.6% (6)	68.4% (13)
Nonsyphilitic	4.0% (2)	16.0% (8)	80.0% (40)
Total:			
Syphilitic	5.0% (4)	31.3% (25)	63.7% (51)
Nonsyphilitic	8.2% (161)	27.9% (546)	63.9% (1,248)

hospital found an observed incidence of coexistence of the two diseases of 0.85 in contrast to an expected incidence of 1.16.

(b) *Extent of tuberculosis by the time the patients have reached the Sanatorium:* When admitted to the Sanatorium for treatment, comparison of the stages of pulmonary tuberculosis in syphilitic and nonsyphilitic patients fails to show an increase in the extent of the tuberculous infection in those patients with syphilis (table 4).

(c) *Course of tuberculosis while in the Sanatorium:* Classification of the patient on discharge shows the result of treatment on his tuberculosis at the end of Sanatorium residence. Comparison of the classification on discharge in the syphilitic and nonsyphilitic patients is made in table 5. Although, unfortunately, some groups are small, the course of the tuber-

TABLE 5

*Classification of tuberculosis after treatment**

	ARRESTED, QUIESCENT OR IMPROVED	UNIMPROVED OR DIED
Admitted as Minimal		
White:		
Syphilitic	100% (4)	0
Nonsyphilitic	91.6% (142)	8.4% (13)
Colored:		
Syphilitic	0	0
Nonsyphilitic	100.0% (2)	0
Total:		
Syphilitic	100.0% (4)	0
Nonsyphilitic	91.7% (144)	8.3% (13)
Admitted as Moderately Advanced		
White:		
Syphilitic	75.0% (12)	25.0% (4)
Nonsyphilitic	80.5% (432)	19.5% (104)
Colored:		
Syphilitic	50.0% (3)	50.0% (3)
Nonsyphilitic	75.0% (6)	25.0% (2)
Total:		
Syphilitic	68.2% (15)	31.8% (7)
Nonsyphilitic	80.6% (438)	19.4% (106)
Admitted as Far Advanced		
White:		
Syphilitic	35.2% (13)	64.8% (24)
Nonsyphilitic	46.4% (561)	53.6% (646)
Colored:		
Syphilitic	15.4% (2)	84.6% (11)
Nonsyphilitic	27.5% (11)	72.5% (29)
Total:		
Syphilitic	30.0% (15)	70.0% (35)
Nonsyphilitic	45.8% (572)	54.2% (675)

* Three syphilitics with moderately advanced tuberculosis and one syphilitic with far advanced tuberculosis, classified in table 4, were discharged as "not treated" and are omitted from this table.

culosis in the syphilitics seems to be slightly less favorable than in the nonsyphilitics. This unfavorable trend appears to be greater in the colored syphilitics than in the white. What is not shown in the table is that it was found that the tuberculosis in those patients with active syphilis seemed to run a more favorable course than in those with latent syphilis. This is extremely interesting, but the group of patients is too small to warrant definite conclusions. It should also be stressed that some of the patients with syphilis had antisyphilitic treatment so that we are dealing not alone with coexisting tuberculosis and syphilis, but with tuberculosis and syphilis plus individualized antisyphilitic treatment.

IS THE BEHAVIOR OF SYPHILIS PECULIAR IN THE PRESENCE OF PULMONARY TUBERCULOSIS?

The behavior of syphilis in tuberculous patients can be judged by the study of the incidence of the development of syphilis, the type of the disease when the patient is admitted and its course while the patient is in the Sanatorium.

(a) *Incidence of development of syphilis in persons with tuberculosis:* Statistics in a previous section show that 4.0 per cent of all admissions to this Sanatorium are definitely syphilitic (table 1). This incidence is essentially the same as that for the general population from which the Sanatorium patients are drawn, suggesting that the prevalence of syphilis in persons with tuberculosis is not greater than in the nontuberculous.

(b) *Type of syphilis in the tuberculous patient on admission to the Sanatorium:* The classification of syphilis on admission (table 3) reveals a distribution of late types of syphilis that is comparable to that found in the syphilis clinics where the great majority of patients are not tuberculous. There were no unusual proportions of active and malignant types of syphilis in our admissions.

(c) *Course of syphilis while the patient was in the Sanatorium:* It was evident that there were no more recurrences, infectious relapses, unfavorable treatment reactions or Wassermann-fast cases in the tuberculous patients in the Sanatorium than are usually found in the venereal disease clinics (tables 3 and 6).

INDICATIONS FOR AND INFLUENCE OF ANTISYPHILITIC TREATMENT

Caution has always been the keynote in the treatment of syphilis in a tuberculous patient. The reason for this has been a fear that ade-

quate and intensive antisyphilitic treatment endangers the tuberculosis. The general practice in the past has been to delay treatment altogether in cases of latent syphilis while the tuberculosis is active and then to treat moderately those patients with chronic fibroid tuberculosis. Potter (1) outlined this conception in 1916, but presented his views almost entirely from the consideration of the tuberculous infection. Later Schlesinger (7) gave a comprehensive discussion of treatment in which he took into account the activity of both the syphilitic and tuberculous infections. This presentation of the subject is worth reviewing and is translated into English in the article of Padgett and Moore (2). This scheme is the one generally followed in the modern treatment of the two diseases. Padgett and Moore wisely emphasized the importance, from the public health standpoint, of immediate treatment of infectious types of syphilis, regardless of the state of the tuberculosis. They also stressed the fact that "certain types of late syphilis (aortitis, aneurysm, paresis) are more surely fatal to the patient if untreated than even exudative tuberculosis and other types are more productive of chronic invalidism than tuberculosis (tabes dorsalis and other forms of neurosyphilis). Even in a symptomless patient, apparently clinically well, the expert syphilologist can often predict with confidence that grave forms of cardiovascular or neurosyphilis will develop in the future if treatment is withheld, and can guard against these developments with appropriate therapeutic methods."

Taking into consideration these opinions and those of other authors and combining with them our own experiences, we have, over the period of years, formulated our own general plan for antisyphilitic treatment of these patients. (*1*) If the syphilitic disease is in an infectious stage, treat it to the point of noninfectivity, no matter what the extent or type of the tuberculosis. (*2*) Should the syphilis be of the latent stage, attention should be paid first to the age of the patient. Patients over sixty can usually be safely allowed to forego antisyphilitic treatment. If the patient is younger, evaluate the pulmonary disease. Do not treat patients with far advanced, progressing tuberculosis who appear to have a hopeless prognosis. If the far advanced disease later shows definite evidence of improvement, antisyphilitic treatment can then be started cautiously. Delay treatment in patients with acute, active or exudative types of tuberculosis, no matter how small the extent of the tuberculosis. Treat patients with previously active pulmonary disease as soon as it becomes quiescent. (*3*) In patients with certain early

manifestations of active late syphilis (aortitis, aneurysm, central nervous system syphilis) treat the syphilis if it is felt that the patient's life may sooner be endangered by syphilitic infection than by his chronic pulmonary tuberculosis. Whereas treatment of syphilis can be delayed in the latent syphilitics while the progress of the tuberculosis is observed, it should be begun at the earliest possible moment in patients with active late syphilis. (*4*) Suspend treatment of syphilis if the patient has febrile reactions, haemoptyses, develops wet pleurisy or shows by X-ray spread of tuberculosis.

Of the 87 patients who had a definite diagnosis of syphilis over the ten-year period, 35 were treated according to the principles just discussed.

TABLE 6

Patients receiving antisyphilitic treatment

	TUBERCULOSIS		SYPHILIS		
Amount of antisyphilitic treatment	Progressed or unchanged	Improved	Serology unchanged	Serology improved	Serology reversed
Poor (15)	7 a	8	12 df	3 g	0
Moderate (11)	2	9 b	7 e	1	3
Good (8)	2 h	6 c	1	4	3

a. Febrile reaction and spread of tuberculosis during treatment (one case).
b. Acute tuberculous appendicitis and haemoptysis during treatment (one case).
c. Spread of disease by X-ray during treatment—later improved (one case).
d. Severe bismuth stomatitis (one case).
e. Progression of aortitis during treatment (one case).
f. Exfoliative dermatitis (one case).
g. Febrile reaction during treatment (one case).
h. Febrile reaction and spread of tuberculosis during treatment (one case).

Sulpharsphenamine (0.45 g.), neoarsphenamine (0.3 to 0.45 g.), mercurosal (0.05 g.) and thiobismuth (0.2 g.) were the drugs used in the first nine and one-half years of study; mapharsen (0.04 g.) and bismuth subsalicylate (0.2 g.) were used the last half year. Usually courses of eight to ten weekly doses of heavy metal were alternated with courses of eight to ten doses of an arsenical. We have designated the amount of treatment as "poor" (less than one course of arsenical and one course of heavy metal), "moderate" (more than one course each, but less than two courses of arsenical and heavy metal) and "good" (two or more courses each of arsenical and heavy metal). The outcome of the tuberculosis and the serological changes in the treated patients are given in

table 6. The groups which received only "poor" or "moderate" treatment are large because they include patients on whom antisyphilitic treatment was begun and who, as their tuberculosis improved, were soon able to leave the Sanatorium, and patients with slowly progressing disease on whom treatment of syphilis was begun, to be abandoned soon afterward as the disease continued to advance. This last group would not be considered satisfactory for treatment in the light of our present knowledge, and is not to be misconstrued as a group showing unfavorable tuberculous reactions from the antisyphilitic treatment itself.

Four out of 25 patients whose tuberculosis was showing favorable change when treatment was begun had unfavorable reactions during the period of their antisyphilitic treatment. One patient had febrile reactions following sulpharsphenamine, her disease progressed and she died. The second developed a tuberculous appendicitis while receiving neoarsphenamine, then improved, later to have a haemoptysis five days following a dose of mapharsen. He is still a patient and his tuberculosis is clearing. A third patient had a slight spread of disease while receiving sulpharsphenamine, then improved and was given several more courses of arsenical and heavy metal three years later without ill effects on his tuberculosis. The fourth patient was a colored woman who had previously done well while receiving two courses of arsenical and four of heavy metal. Following the first dose of bismuth in a fifth course she had an extensive spread of tuberculosis and has since done poorly. Thus out of 25 patients whose tuberculosis was showing improvement, 3 had unfavorable reactions while receiving arsenicals and one while receiving a heavy metal. In 2 of the 4 the tuberculosis later improved.

The serological response of the cases of syphilis to treatment is also shown in table 6 and is what is to be expected, with more of the better treated patients manifesting favorable changes. Four patients had unfavorable complications not related to their tuberculosis. One was an old colored man with aortitis who developed a severe bismuth stomatitis after eight weekly injections of 0.15 g. of bismuth subsalicylate. One white man's aortitis seemed to become more pronounced while receiving a course each of sulpharsphenamine and mercurosal. Antisyphilitic treatment was discontinued when he left against advice. He was readmitted and died eight years later from advanced pulmonary tuberculosis. One patient in the treated group developed a mild dermatitis after the third injection of sulpharsphenamine, this was probably an arsenical exfoliative dermatitis. She later had a course of heavy metal

and her tuberculosis showed marked resolution during her stay. A fourth patient had slight elevations of temperature and pulse following injections of sulpharsphenamine, but showed no spread of tuberculosis by X-ray. Antisyphilitic treatment was abandoned in this patient and his tuberculosis continued to improve.

SYPHILIS OF THE LUNG

Syphilis of the lung occurring in the atelectatic lungs of still-born and short-lived congenital syphilitic babies (*pneumonia alba*) is relatively frequent and spirochetes can often be demonstrated in these lungs in large numbers. Syphilitic ulceration and scarring of the larynx in the adult is also recognized, but there is controversy as to whether similar lesions can exist in the trachea and bronchi. On the other hand, acquired syphilis of the lung itself is an entirely different question. This manifestation of the disease is a rarity. Diagnosis of pulmonary syphilis is extremely difficult, even by the pathologist. Carrera (8) studied 152 autopsy cases of syphilis and found pulmonary lesions that he felt were syphilitic in 12. Five of these were described as gummata with peribronchial lesions and arteritis; 7 showed fibrosis and arteritis. His descriptions of the pathological findings are detailed and his bibliography extensive. Other pathologists, however, contend that syphilitic necrosis and fibrosis in the lung cannot be distinguished macroscopically and microscopically with certainty from the necrotic and fibrotic changes caused by other disease processes. Only a handful of men have ever been able to demonstrate spirochetes in microscopical sections of the lung and then only in a very few, scattered cases (Levaditi, *et al.* (9), Koch (10), Kielty (11), Schmorl (12), Warthin (13)).

The work of these pathologists has apparently proved that syphilis of the lung, though rare, does exist. Howard (14) describes five forms of pulmonic syphilis: gummata, chronic interstitial pneumonia, pulmonic sclerosis, syphilitic phthisis and bronchopneumonia. He also presents the following diagnostic criteria: absence of grave symptoms, sputum persistently negative for the tubercle bacillus, other evidence of syphilis in the body, positive serological tests for syphilis and the finding of spirochetes in the sputum. He adds that only an expert parasitologist could hope to distinguish between the *treponema buccalis* and the *treponema pallida*.

In reality, definite clinical diagnosis of syphilis of the lung is impossible. The symptomatology described by various authors may be confused with

that of tuberculosis or bronchiectasis or cardiac disease. In doubtful cases, tubercle bacilli are being found more frequently now than before by use of present day methods of concentrating sputum and examination of stomach contents following gastric lavage. The X-ray picture sometimes ascribed to pulmonary syphilis cannot be distinguished from similar shadows found in tuberculosis, mycotic infections of the lung, bronchiectasis or various types of pneumonoconiosis. Osler (15) stated that "the therapeutic test upon which so much reliance is placed is by no means conclusive." The lesion may resolve or remain stationary under treatment, whether it be syphilis or some other disease.

In the 106 patients that had positive or doubtful serological tests when admitted to the Sanatorium there was not a single one that could be diagnosed as having syphilis of the lung.

COMMENT

Previous reports have given the percentage of tuberculous patients with syphilis as varying from 3 per cent (Koester and Amend (16)) to 19 per cent (Letulle, Bergeron and Lepine (17)). The incidence of syphilis in admissions to this Sanatorium approximates the collected statistics from fifty Sanatoria by Guild and Nelson (18) in 1936. They found a total of 6.5 per cent with 4.1 per cent of the white and 21.0 per cent of the colored patients showing a positive blood test. At Laurel Heights 4.0 per cent of the total admissions, with 3.2 per cent of the white and 26.0 per cent of the colored patients, were diagnosed as syphilitic.

In attempting to judge the behavior of pulmonary tuberculosis in the presence of syphilis, it was pointed out that the incidence of active tuberculosis in syphilitics is not greater than in nonsyphilitics. Also it was shown (table 4) that the extent of the tuberculosis was practically the same in the two groups when they were admitted to the Sanatorium. However, pulmonary tuberculosis in the syphilitic patients did not respond as favorably to sanatorium treatment as did the disease in the nonsyphilitics. An explanation for this cannot be given.

Antisyphilitic treatment might be suspected as the cause of the poor showing among the syphilitics. It is extremely difficult to decide if the administration of antisyphilitic drugs can be responsible for unfavorable changes in the course of pulmonary tuberculosis. Patients can be selected carefully for treatment and the drugs given with caution and still a spread of the phthisis may occur. Yet remissions are notorious in

uncomplicated tuberculosis itself. So even with all the facts of a given case at hand it is usually impossible to say whether the increase in the pulmonary disease was to be expected by the law of possibility or was the direct result of antisyphilitic treatment.

Padgett and Moore (2) felt that the administration of an arsphenamine had provoked the flare-up and rapid dissemination of previously quiescent and clinically unrecognizable pulmonary tuberculosis in 15 of their patients. Habliston and McLane (19) claimed no untoward results from treatment. Other authors (Giese and McGovern (20), Gallant (21), Sullivan (22) and Smith (3)) have felt that beneficial effects on the tuberculosis have been obtained by cautious treatment of the syphilis. Unfortunately there is a fault common to all of the statistical evidence from sanatoria comparing results between treated and untreated syphilitics. All these patients were treated conservatively. Thus patients with more unfavorable tuberculous disease were purposely not given antisyphilitic treatment. This group of patients, because of their extensive and active tuberculosis, naturally showed a high death rate and generally unfavorable results. On the other hand, patients with good prognosis were the ones singled out for treatment of their syphilis. Their pulmonary disease could be expected to show more favorable courses. No one has had a large enough group of patients with the coexisting two diseases to be able to give antisyphilitic treatment to alternate patients with favorable and alternate patients with unfavorable types of tuberculosis. This would establish a group of controls for comparison. At present the question of the effect of antisyphilitic treatment on tuberculosis is unanswered.

SUMMARY

1. In 2,160 admissions to the Laurel Heights State Tuberculosis Sanatorium there were 106 (4.9 per cent) patients who gave positive or doubtful serological reactions for syphilis. A definite diagnosis of syphilis could be made upon 87, or 4.0 per cent. Of the white patients 3.2 per cent and of the colored 26.0 per cent were syphilitic.

2. A classification of the stage of the syphilitic infections on admission is given. The majority were in the late latent group.

3. Pulmonary tuberculosis in the syphilitic patients did not respond as favorably to sanatorium treatment as did the disease in the nonsyphilitics.

4. The course of the syphilis in patients with tuberculosis does not appear to differ from the course of the disease in the nontuberculous.

5. Indications for treatment of syphilis are outlined, taking into account the activity of both diseases. The results of treatment in 35 patients are presented. The question of the influence of antisyphilitic treatment on the course of tuberculosis cannot be answered. The response of syphilis to antisyphilitic treatment appears to be the same in nontuberculous and tuberculous patients.

6. Syphilis of the lung is a rarity. It cannot be definitely diagnosed clinically.

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THE EVOLUTION OF HAEMATOGENOUS PULMONARY TUBERCULOSIS INTO BRONCHOGENIC TUBERCULOSIS[1]

SAMUEL COHEN

The concept of tuberculosis as a systemic disease is an established and fundamental one in the elucidation of many of its varied manifestations. Furthermore, the literature, particularly of the past decade, reveals increasing recognition among clinicians that pulmonary tuberculosis is often part of this systemic infection. In other words, in addition to exogenous reinfection, endogenous reinfection of the lungs may occur from preëxisting sources of bacilli. Lesions, for example, in the bones, joints, genitourinary tract, brain, etc. are readily conceded as haemic implants; why should the lungs which are large filter beds escape the effects of blood-borne dissemination?

When such a postprimary spread takes place, the source is usually an incompletely healed component of the primary complex, most commonly a caseous lymph node situated in the mediastinum. The caseous material may rupture directly into the vascular tree, or spread may occur by means of a progressive lymphadenitis into the main lymphatic trunks with invasion of the venous circulatory system and dissemination into the lungs, among other organs of the body. Foci elsewhere, of course, can contribute bacilli in a similar mechanism.

At this point, it is well to refer to the factors, according to Grethmann (1), which determine the pathogenesis of haematogenous tuberculosis in general: (*1*) the anatomical structure of the involved organ or organs; (*2*) the topographical location of the "feeding focus" or the source; (*3*) the dose (small or large) of tubercle bacilli and tuberculotoxins reaching the various structures; (*4*) the frequency with which this disseminated material is discharged; (*5*) the fate of the resultant lesions—regression or progression. The pathological pulmonary "set-up," of course, is likewise guided by this pattern. The traditional pathological and roentgenological appearances are seen in those instances of acute gener-

[1] From the Tuberculosis Service of Dr. B. S. Pollak, Medical Center, Jersey City, New Jersey.

alized haematogenous miliary tuberculosis of the lungs due to the dissemination of a single massive fine suspension of organisms. Less dramatic and less well recognized are cases of subacute, chronic or intermittent bacillaemia. It is in these groups of patients that haematogenous pulmonary tuberculosis may unfold an interesting and intriguing story which should stir the vision of the clinician.

Cases in which progression of haematogenous lesions within the lungs occurs with ultimate bronchogenic extension have been described by Grethmann (1) and Miller (2) as transitional forms. Careful prolonged observation of tuberculous cases will reveal examples where the evolution from lympho-haematogenous into bronchogenic dissemination is evident and will confirm the validity of the designation mentioned above. That such a series of events may and does occur is conceded by practically all pathologists. Colored patients, particularly, in view of their increased tendency for vascular spread and relatively poor resistance to the disease, constitute valuable clinical material in forging this pathogenetic link. My purpose in this paper is to illustrate by a few detailed case reports the evolution from haematogenous pulmonary tuberculosis into bronchogenic phthisis, especially from a roentgenological point of view.

A simple and brief preliminary résumé of pertinent general observations is first indicated.

I. THE PATHOLOGY AND EVOLUTION OF HAEMATOGENOUS TUBERCULOSIS

The appearance of lympho-haematogenous pulmonary tuberculosis will vary with the type and phase of the disease process in which the patient is first seen. The characteristic early pattern of the pulmonary foci is the formation of tubercles (exudative, productive or mixed) situated in the interstitial tissue and most commonly distributed in a symmetrical manner. Now, in cases of acute generalized miliary tuberculosis involving the lungs, these tubercles are of millet seed size and extend rather uniformly from the apices to the bases; chronic generalized miliary tuberculosis of the lungs shows a similar apportionment of these tubercles in the absence of acute clinical manifestations; focal miliary pulmonary tuberculosis, where the dose of organisms is small, produces miliary lesions which are usually confined to the upper portions of the lung fields; this is fairly frequent. However, in protracted haematogenous multiform tuberculosis, the pulmonary foci, like the lesions elsewhere, may vary from miliary to large conglomerate nodules, due largely to repeated bacillary implantations of different dosage. In all

of these types, but more particularly the latter, involvement of the pleura is common.

Also, in all, the fate of the parenchymal lesions is either healing (complete or incomplete) or progression. The former may take place by: (*1*) resolution; (*2*) fibrosis, resulting in thickening of the alveolar septa with round cell infiltration and fibrosis of the interstitial tissue—the surrounding alveoli may vary in size, some normal, others atelectatic and still others emphysematous; (*3*) calcification, which occurs only in caseous lesions. On the other hand, there is pathological evidence that the interstitial tubercles may coalesce, caseate and excavate with subsequent extension of the disease through the intracanalicular channels. This may develop shortly after their localization or months or years later. Some writers have referred to the "punched out" shallow cavity in these cases, but it is not pathognomonic of a haematogenous derivation. The lungs may finally show a preponderance of bronchogenic lesions with interspersed discrete haematogenous foci which bear no relation to the bronchial tree.

II. ROENTGENOLOGICAL APPEARANCE

In the types of cases under consideration, the early haematogenous pulmonary lesions may appear on the roentgenogram as: (*1*) more or less discrete bilateral miliary foci, frequently symmetrically arranged and usually in the upper parts of the lungs; (*2*) larger nodules of different sizes or softer patches in a less regular distribution; the diversity in their appearance presupposes varied dosage of tubercle bacilli lodging in the lungs and different specific reactions; (*3*) fine, reticular, strand-like infiltration, again rather evenly arranged along the bronchovascular markings. Miller (3) believes the lesions in these instances may be due to spread along the lymphatics in the interstitial tissue. Widening of the hilar zones and of the mediastinum may be present due to enlarged lymph nodes. Evidence of pleuritis (recent or old) is frequently seen. It is sometimes an important precursory sign on the X-ray film of a haematogenous dissemination. A flat abdominal plate may be of interest and reveal calcified or partly calcified mesenteric or retroperitoneal nodes which may be the possible source for the endogenous reinfection; Grethmann (4) also called attention to the possible roentgenological visualization of calcification within the spleen as evidence of an old systemic spread.

As previously mentioned, these pulmonary foci may retrogress in any one or a combination of three ways with roentgenological changes of

clearing, strands or nodules of fibrosis or calcified areas. When the lesions however terminate in bronchogenic tuberculosis, confluence of the foci occurs; further progression leads to formation of cavities which are usually shallow and thin-walled at first; thereafter with increasing bronchogenic spread, the roentgen film may show a variety of shadows. *In this later state, the differentiation of the disease process radiographically from the simple progressive exogenous reinfection lesion is very difficult if not impossible. Its haematogenous origin may be entirely unsuspected.* The roentgenogram may be further complicated in some cases by repeated endogenous implants, and the dissociation, on a given single film, between the bronchogenic and haematogenous infiltrative lesions in the late or terminal stage of these transitional cases is also well-nigh impossible.

III. SYMPTOMS AND SIGNS

Except in cases of acute generalized haematogenous tuberculosis, the pulmonary and constitutional symptoms, at first, are not striking. Development of pleurisy with effusion may frequently precipitate the patient's first visit to a physician. Often the onset is insidious, however. Cough and expectoration increase as the transition from haematogenous to bronchogenic tuberculosis proceeds; and the sputum which is negative for acid-fast bacilli at the outset (inasmuch as the early tubercles are interstitial and in a closed system) becomes positive in the later stage when confluence and cavitation occur. Intracanalicular spread may then cause the familiar complications of tuberculous laryngitis and enteritis. Haemoptysis may occur with ulceration. Also constitutional symptoms, anorexia, loss of weight, fever, etc., become more noticeable with bronchogenic spread.

Abnormal physical signs are scanty in early haematogenous dissemination but are more evident after extension through the bronchi has taken place. Besides the strictly pulmonary findings, attention should be focussed on discovering frequently associated manifestations: (*a*) involvement of the serous membranes, particularly the pleura; (*b*) palpably enlarged superficial lymph nodes; (*c*) extrapulmonary haematogenous lesions; (*d*) enlarged spleen.

IV. CLINICAL DIAGNOSIS

The first point to decide is whether the original lesion in the lungs is the result of haematogenous dissemination. Pinner (5) stated absolute proof cannot always be given but he mentioned the following criteria for

assuming a haematogenous genesis: "(*1*) the roentgen findings of more or less evenly distributed lesions; (*2*) the frequent absence of older pulmonary foci from which a bronchogenic spread could have occurred; (*3*) the frequent association of extrapulmonary haematogenous lesions." The following are the most common nontuberculous conditions which may simulate on the roentgenogram haematogenous pulmonary tuberculosis in some respects (however, there are usually some differential radiological points and any remaining doubt should be dispelled by a competent clinical examination of the patient): (*a*) silicosis; (*b*) cases of cardiac decompensation which have had repeated episodes of passive congestion of the lungs with some fibrosis and usually associated with pleuritic changes; (*c*) pulmonary fibrosis, regardless of aetiology, especially when bilateral and situated in the upper segments of the lung fields; (*d*) miliary carcinomatosis.

An antemortem diagnosis of the transition from haematogenous into bronchogenic tuberculosis can best be made by comparison of frequent serial roentgenograms with especial attention to the features previously mentioned. Frequently, one encounters cases with X-ray evidence of cavitation and finely disseminated bilateral infiltrative foci which may closely resemble the pattern outlined above for the transitional forms. These foci most often represent a "bronchogenic nodular and miliary spread" (Grethmann and Amberson (6)) from an older cavity and commonly result from an antecedent pulmonary haemorrhage due to a relatively fine suspension of tubercle bacilli in the aspirated blood. Comparison of serial X-ray films and the history of haemoptysis usually suffice to make the differential diagnosis.

However, it is only fair to state that the transition from haematogenous into bronchogenic tuberculosis cannot always be sharply demarcated. As Miller (7) noted, "Within the range of clinico-pathological processes standing between the clear cut haematogenous miliary dissemination into the lung and the clear cut chronic isolated bronchogenic phthisis, there must exist very numerous pictures representing fluent transitions between the two end poles. It is to be expected that the clinical process will bear the stigmata of either haematogenous or bronchogenic origin, according to their place in the above mentioned transition and the recurrent blood-stream dissemination with intervening bronchogenic spreads will tend to produce a great deal of overlapping which makes for further complications that increase the difficulties of delineation of the clinical pictures."

CASE REPORTS

Case 1: A. D., a colored female, age 17, was admitted to the Tuberculosis Service July 31, 1935. She had been attending the clinic for the past five years as a follow-up contact case. The tuberculin test was positive in 1930 and the chest roentgenograms of April 29, 1930 and July 25, 1934 were essentially negative. In December, 1934, she contracted so-called "flu" with pain in the right posterior chest. Fatigability and anorexia soon appeared with loss of 13 pounds by July, 1935. It was at this time that a dry cough was noticed.

The patient was thin and chronically ill appearing. Lymph nodes in the neck region were palpable. The right lung showed dulness throughout except at the base posteriorly where flatness prevailed; a friction rub was audible and the breath sounds were very diminished. The left lung was negative. The sputum was negative for tubercle bacilli and the Wassermann reaction was negative.

The chest film of August 6, 1935 (figure 1) revealed a widening of the superior mediastinum, due to enlarged nodes; the right diaphragm was flattened and the costophrenic angle obliterated. An increase in linear markings was noted with possible few fine foci in the first left anterior interspace. Evidence of an increasing effusion soon appeared and straw colored fluid was aspirated from the right pleural cavity. The first unequivocal evidence of parenchymal disease appeared in the X-ray film of November 27, 1935 (figure 2) as predominantly fine nodular infiltration from the first to the third anterior interspaces on either side. An area of increased density in the right hilum region was noted. In December, 1935, enlarged bilateral axillary nodes were felt which gradually increased to the size of a hen's egg. The roentgenogram of March 7, 1936 (figure 3) showed added infiltrations, rather symmetrically distributed with some tendency to confluence in the second left anterior interspace and the third right anterior interspace. The superior mediastinal shadow was also more prominent than on the admission film. An irregular low grade fever persisted. The cough was productive of two drams of sputum and several sputum concentrations were negative until May 4, 1936, when tubercle bacilli were first reported. On the roentgenogram of May 20, 1936 (figure 4) further scattered infiltrations in both lung fields with small annular shadows in the second and third right anterior interspaces were visualized. Note the "pouting" in the axillae due to the adenopathy.

In the latter part of May, palpation of the abdomen revealed a firm, tender nodule to the right of the umbilicus and a smaller one in the left upper quadrant. These became larger and were considered as abdominal lymph nodes. Intermittent periods of abdominal pain and diarrhoea also occurred and the patient lost weight steadily. The chest film of August 27, 1936 (figure 5) showed progressive increase in the patchy mottled, predominantly exudative foci of varying size with scattered intervening multiple areas of cavitation.

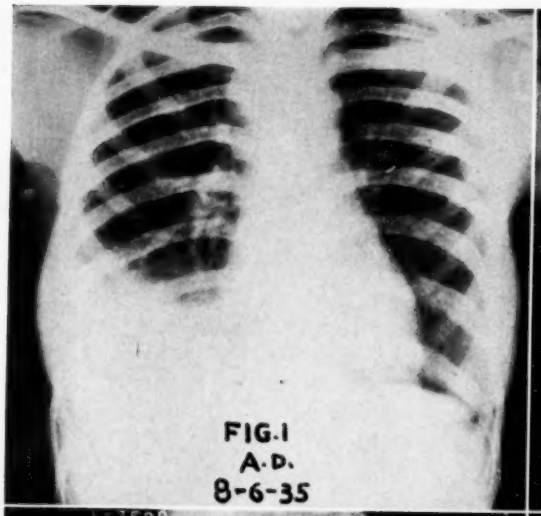
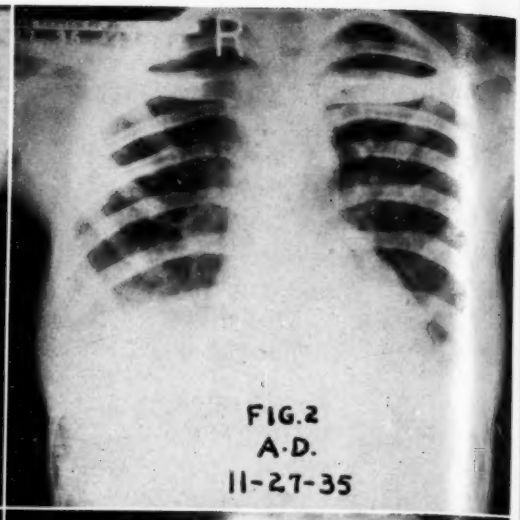


FIG.1
A.D.
8-6-35


R
FIG.2
A.D.
11-27-35

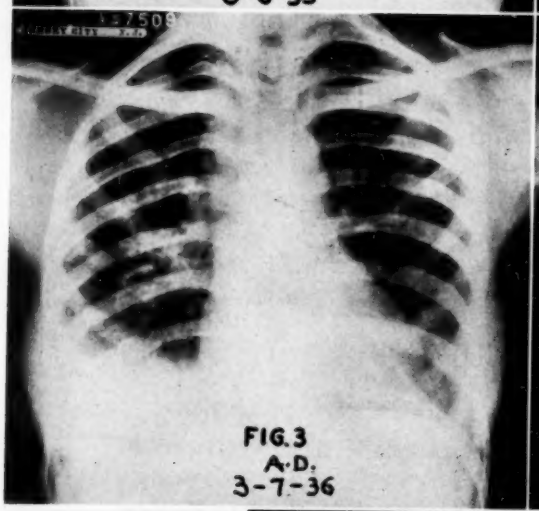


FIG.3
A.D.
3-7-36

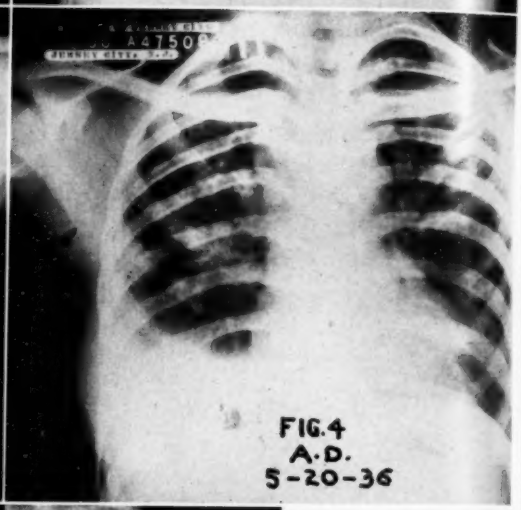


FIG.4
A.D.
5-20-36

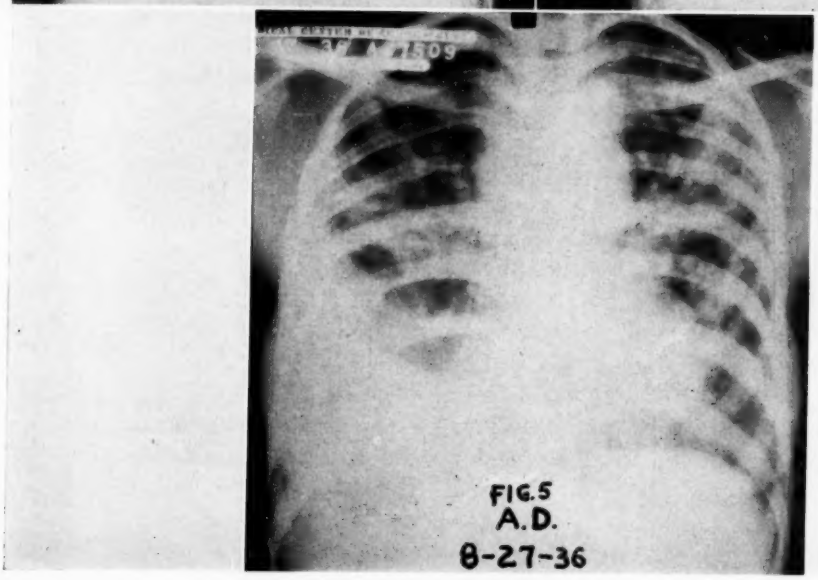


FIG.5
A.D.
8-27-36

FIGS. 1–5

Reaccumulation of fluid in the right pleural cavity appeared and the mediastinal density again became wider. Oedema of the ankles and dyspnoea appeared in August, 1936. During this month and September, the fever was at a higher level, at times up to 103°F. Physical examination just prior to death disclosed coarse râles throughout both lung fields with amphoric breath sounds in the left upper lobe. The heart sounds were rapid, regular and of poor quality. The spleen was not felt. It was believed the patient's orthopnoea was aggravated by pressure of the mediastinal lymph nodes on the trachea and large bronchi. The patient died October 1, 1936.

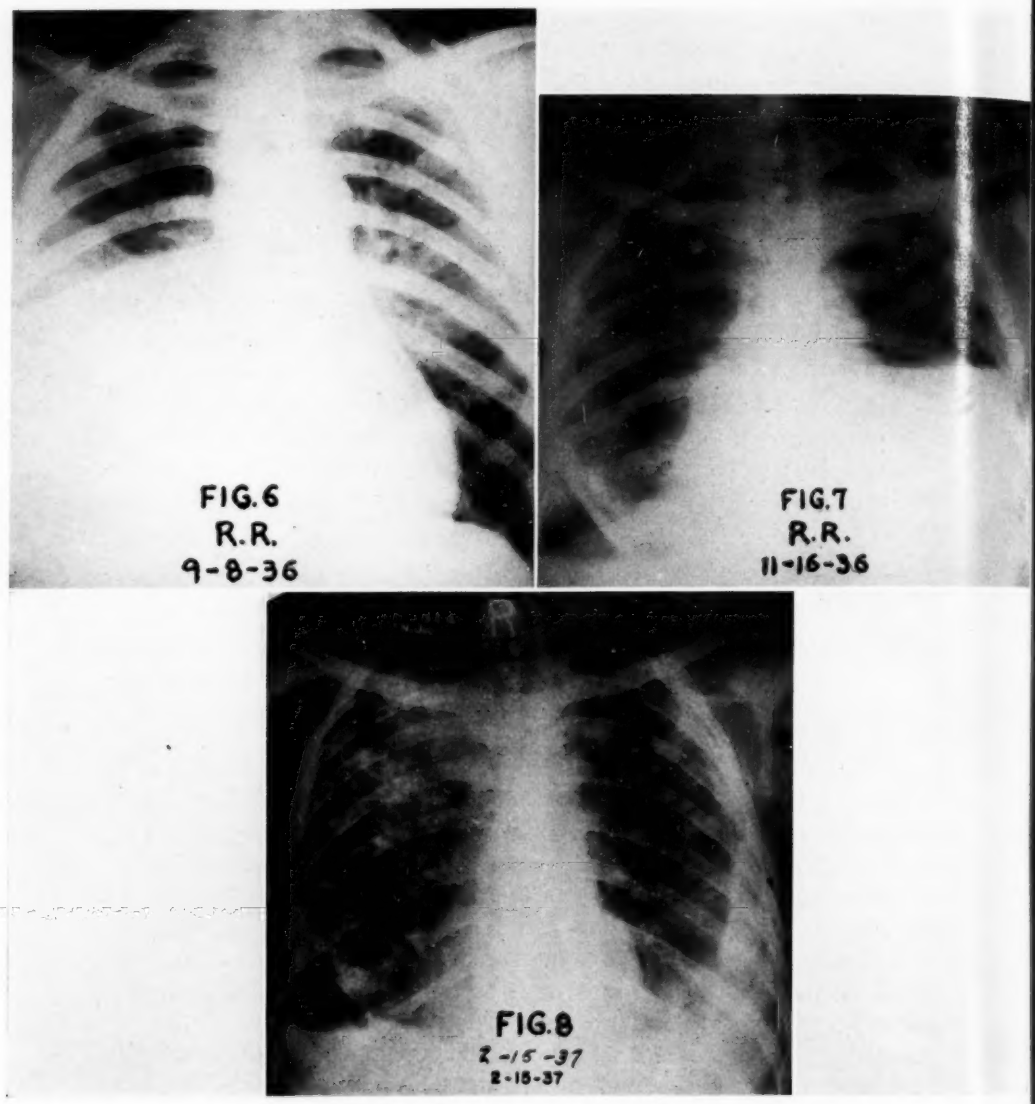
Comment: This patient was under close hospital observation for fourteen months and it seemed quite obvious that we were dealing with a case of protracted lympho-haematogenous tuberculosis. Of great interest was the clinical evidence of progressive, active tuberculous adenitis involving superficial and deep (mediastinal and abdominal) lymph nodes. Involvement of the serous membranes was less striking. Flat abdominal films did not show any calcified lymph nodes or calcified foci in the spleen.

In view of the patient's race, the presence of wide-spread adenopathy and the roentgen appearances, the original source of the early pulmonary lesions as of endogenous reinfection would appear to be unquestioned. The patient probably had a chronic or recurrent tuberculous bacillaemia, and most likely repeated bacillary feedings took place into the lungs. Physical signs in the chest and serial roentgenograms subsequently indicated progression by bronchogenic extension also.

Case 2: R. R., a colored male, age 35, was admitted to the Tuberculosis Service February 15, 1937. In January, 1936, the patient noticed fatigability, anorexia, weakness and cough. With the development later of dyspnoea, he entered the Medical Service in September. The chest film of September 8, 1936 (figure 6) showed a widening of the superior mediastinum to the right (due to lymph nodes) with fine, nodular and strand-like infiltration along the bronchovascular markings in the first and second anterior interspaces on the right and in the first three anterior interspaces on the left. A pleural effusion was also present on the right side.

The patient signed a release on October 22 but reëntered the Medical Service four days later because of increased fever and shortness of breath. The chest film of November 16, 1936 (figure 7) revealed evidence of a bilateral hydropneumothorax more marked on the left side with an increase in the infiltrative involvement in the right lung. Straw colored fluid had been previously aspirated from both pleural cavities and replaced by some air. The fluid

aspirated on January 12, 1937 was reported positive for tubercle bacilli. The patient left the hospital the same month and returned for the third time on



FIGS. 6-8

February 4, 1937, being transferred to the Tuberculosis Service February 15, 1937. Now, the patient was definitely more dyspnoeic, he coughed more

and expectoration had increased to four ounces of sputum daily. It was blood-streaked on February 7, 1937. He lost weight and noticed some dysphagia for the past two months.

The patient was emaciated, dyspnoeic and orthopnoeic. Over the right lung dulness was present anteriorly from the apex to the second anterior rib and in the axilla with coarse râles in these areas and over the upper lobe posteriorly; shifting dulness was also present. Over the left lung there was dulness in the supraclavicular fossa, below the third anterior rib, in the axilla and throughout posteriorly. Bronchial breathing was heard at the base of the upper lobe posteriorly with coarse râles in this latter lobe; shifting dulness was elicited. The liver edge was percussed two fingers below the costal margin; the spleen was not felt. Few tiny lymph nodes in the left axilla and bilateral inguinal nodes were palpable. The sputum was positive for tubercle bacilli; the Wassermann test was four plus. The haemoglobin was 55 per cent.

On the day of transfer to the Tuberculosis Service, fluid was again aspirated from the left pleural cavity with slight relief of dyspnoea. The roentgenogram of February 15, 1937 (figure 8) revealed disseminated bilateral predominantly exudative and confluent foci with interspersed annular shadows. A small residual hydropneumothorax on the right and an effusion on the left were also present. Widening of the superior mediastinum persisted. A flat abdominal film was negative. The temperature ranged between 98° and 103°F. The patient died March 2, 1937.

Comment: While the progression of disease in this case of protracted lympho-haematogenous tuberculosis was more rapid than in the preceding one, the roentgenological features were very similar. The conversion of haematogenous pulmonary tuberculosis into the bronchogenic type as visualized by serial X-ray plates of the chest was unmistakable.

Case 3: R. S., a 27 year old Negress, was admitted to the Tuberculosis Service September 23, 1935. In 1926 the patient developed impaired vision and then attended the Eye Clinic for about two years. The vision improved with the administration of eye drops. Also in 1926, the patient experienced migratory pains for a period of three months in both wrists, knees, ankles and finger joints. These were never swollen or red. In March, 1928 the patient was referred to the Tuberculosis Clinic. The tuberculin test was positive. The Wassermann reaction was negative. An X-ray film of the chest on March 20, 1928 (figure 9) showed considerably increased densities in both hilar zones indicative of bronchopulmonary adenopathy. There was slight but definite fine nodular and linear infiltration along the markings on either side from the first to the fourth anterior ribs. Portion of the horizontal fissure was noted in the third right anterior interspace. The patient attended the out-patient

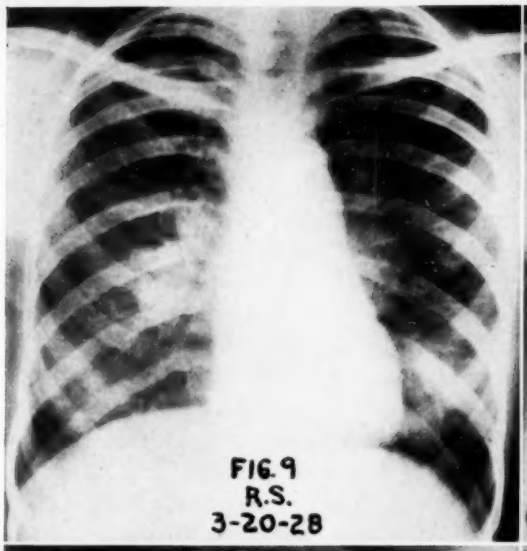


FIG. 9
R.S.
3-20-28

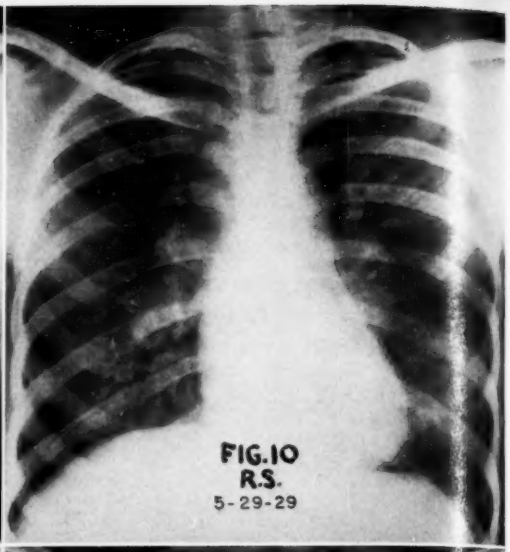


FIG. 10
R.S.
5-29-29

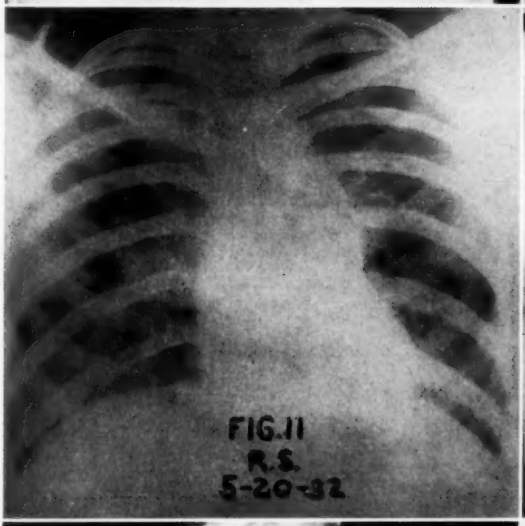


FIG. 11
R.S.
5-20-32

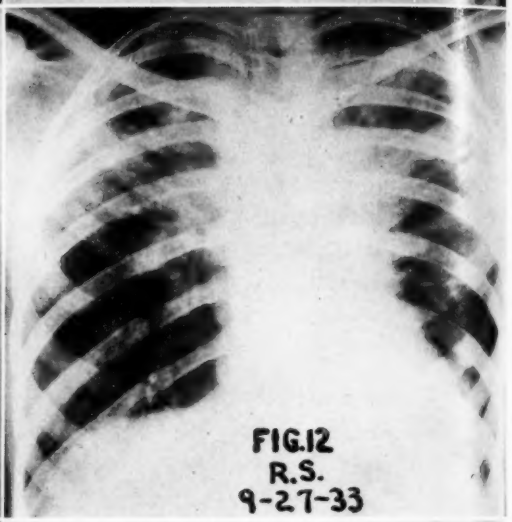


FIG. 12
R.S.
9-27-33

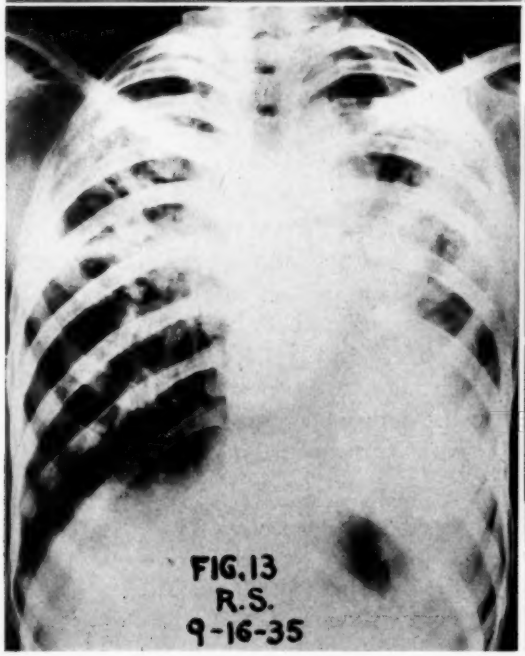


FIG. 13
R.S.
9-16-35

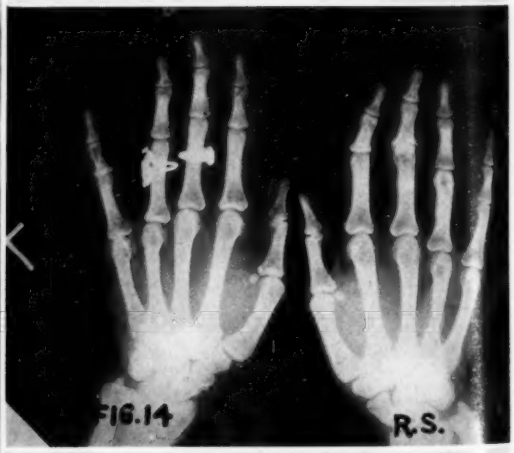


FIG. 14
R.S.

FIGS. 9–14

department at irregular intervals, having been advised on several occasions to enter the hospital. A review of the roentgenograms of the chest up until her first admission in 1935 revealed illuminating changes. The film of May 29, 1929 (figure 10) showed slight recession of the hilar shadows noted in 1928, but now there was definite widening of the superior mediastinal shadow to the right, again evidence of enlarged lymph nodes. There was a slight increase in the parenchymal infiltration. The subsequent film taken three years later, May 20, 1932, (figure 11) revealed bilateral, symmetrically arranged, predominantly productive, strand-like and fine infiltrations; the hilar densities were still prominent. The cardiac shadow showed some loss of its previous convex contour. On the roentgenogram of September 27, 1933 (figure 12) the silhouette of the heart showed straight borders (probably due to pleuropericardial adhesions) and the previous hilar densities were not distinctive. There was no significant change in the lung fields. Since 1933, the patient had a rather persistent cough which at the time of admission in 1935 was productive of one to two ounces of mucopurulent sputum; haemoptysis had never occurred. Dyspnoea began in 1934. The appetite was fairly good and her weight was 94 pounds on entrance to the hospital. Her maximum weight had been 108 pounds. She stated that she had a total of six "blood tests" (Wassermann tests) at varying intervals, all of which were negative.

The patient was underweight and appeared chronically ill. Corneal opacities were noted in both eyes, more marked on the right. Over the right lung there was dulness anteriorly to the second anterior rib, in the upper half of the axilla and posteriorly at the base; bronchovesicular breathing with few râles was heard below the clavicle. Similar auscultatory changes were noted between the fourth to seventh vertebral spines posteriorly. Over the left lung dulness was present over the upper lobe anteriorly and posteriorly, with coarse râles below the clavicle. Moist râles with bronchovesicular to bronchial breathing were audible over the upper part of the lower lobe posteriorly. There was a visible pulsation over the pulmonic area. A long harsh systolic apical murmur was heard which was interpreted as a traction murmur. The second pulmonic sound was greater than the aortic sound. The spleen and liver were not felt. The large joints showed no gross abnormalities and there was no impairment in function; some thickening of the second phalangeal joints in both hands was observed. Bilateral epitrochlear and inguinal nodes were palpable; also a node the size of a lima bean in the left axilla. Wassermann reactions (including a provocative test) were negative. Several sputum examinations were reported negative for tubercle bacilli; however, a gastric lavage was positive.

The patient's course in the hospital was uneventful. The temperature ranged between 98° and 99.8°F. A chest film of September 16, 1935 (figure 13) showed the heart retracted to the left; the right diaphragm was irregular and

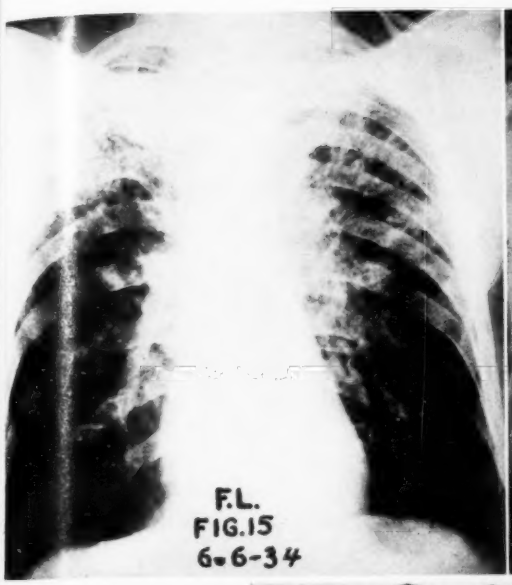
the left was not clearly made out. The lung fields showed scattered bilateral infiltration with a number of areas of "high-light" from the apices to the third anterior ribs on either side. The patient signed a release November 4, 1935. She subsequently died at home in December, 1935.

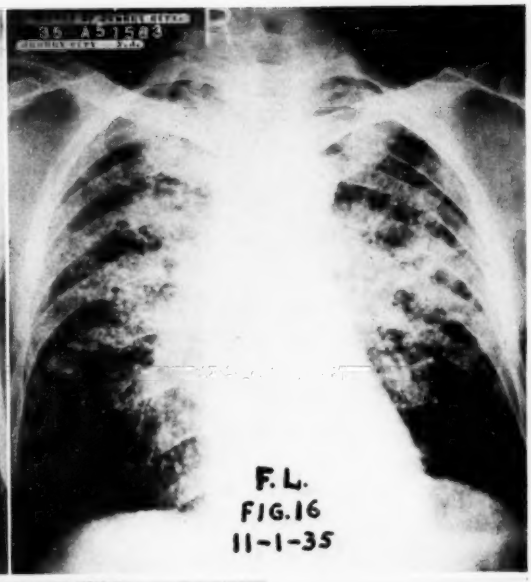
Comment: This case of protracted lympho-haematogenous tuberculosis was most instructive. The chronic iridocylitis was probably on a tuberculous basis. An X-ray film of the hands on October 2, 1935 (figure 14) revealed interesting cystic and productive changes involving several of the phalanges. A diagnosis of *osteitis cystica multiplex,* an atypical form of tuberculosis, was made by the roentgenological department. X-ray plates of the knee joints and ankles were negative. The serial roentgenograms of the chest over a period of seven years were most illuminating. The fate of the intrathoracic lymphadenopathy, the chronicity of the pulmonary lesions with ultimate transition into bilateral apical cavities were striking. This case might be considered by some as the sarcoid type despite the absence of skin lesions.

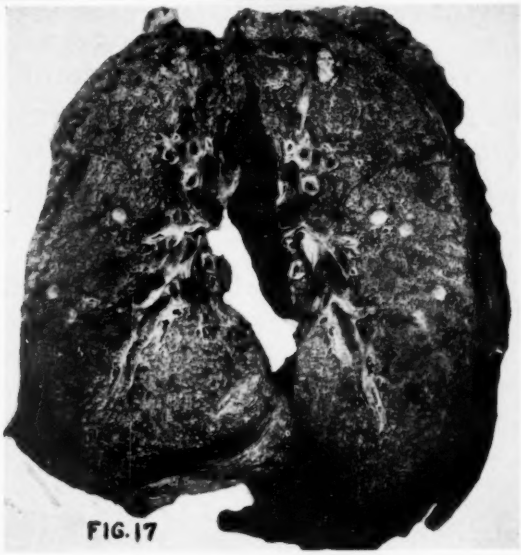
Case 4: F. L., a white male, age 57, was admitted to the Tuberculosis Service October 31, 1935. In the latter part of 1924, he developed stomach trouble and noticed loss of weight. An X-ray film of the chest on December 18, 1924 showed slight fine nodular and linear productive infiltrations in the second right anterior interspace. He entered a sanatorium in January and was discharged after six months, having gained 25 pounds. The patient worked at intervals thereafter and came to the clinic very irregularly for observation. The next roentgenogram of June 6, 1934 (figure 15) revealed bilateral fine seeding and productive strands of infiltrations in the upper portion of both lung fields, more marked on the left. In the early part of October, 1935, he noted pain and then swelling of the left knee. Because of this and the gradual loss of weight, he again attended the clinic and hospitalization was advised.

On admission the patient looked chronically ill. There was dulness throughout the right lung with bronchial breathing over the upper lobe posteriorly and to the second anterior rib; coarse râles were present in these areas and in the apex of the axilla. Similar findings were elicited over the left lung. The liver percussed two fingers' breadth below the costal margin; and there was a questionable enlargement of the spleen. Swelling of the left patella and limitation of motion were noted. Left axillary nodes were felt. The sputum was positive for tubercle bacilli; secondary anaemia was present.

The X-ray film of November 1, 1935 (figure 16) showed disseminated symmetrically arranged miliary-like foci with some confluence and softer mottling near both hilar regions. Small areas of "high-light" were seen in both apices, particularly the left. On November 8, a reddened, firm, swollen epididymis







FIGS. 15–17

was palpable; the seminal vesicles were indurated and the prostate was hard, nodular and enlarged. Pyelographic studies were reported negative for renal tuberculosis. No tubercle bacilli were found in the catheterized ureteral specimens. The flat abdominal plate did not show any calcified nodes. The

patient's general condition became worse; his temperature fluctuated between 100° and 103.4°F. Another roentgenogram of December 17 showed no significant change over the preceding one. Several days before death, he became disoriented, incontinent, semicomatose and more dyspnoeic. Meningitis was suspected and a spinal tap yielded clear fluid under increased pressure with a count of 140 cells; tubercle bacilli were cultured from this fluid. The patient died January 1, 1936.

Autopsy findings: The important postmortem findings were: (*1*) lungs (a) chronic ulcerative tuberculosis with bronchogenic dissemination, (b) haematogenous miliary and confluent miliary nodules, (c) emphysema and anthracosis; (*2*) spleen, kidneys, adrenals: miliary tuberculosis; (*3*) prostate: caseous tuberculous foci varying from approximately 0.5 to 1.0 cm. in diameter; (*4*) left epididymis: similar caseous lesions; (*5*) caseous mesenteric adenitis and chronic ulcerative enteritis. The skull was not opened.

Comment: The abdominal symptoms in 1924, in retrospect, may have been due to the mesenteric nodes. This case, at first, was essentially one of chronic haematogenous miliary tuberculosis of the lungs. The roentgen findings of the chest in 1934 particularly appeared characteristic of a vascular spread. By the time of admission, progression with some degree of cavitation and bronchogenic extension had occurred (as evidenced by positive sputum) and a further superimposed haematogenous seeding was now apparent as part of an acute generalized dissemination. In a section through the left lung (figure 17) are seen apical cavitations, round caseous foci, densely packed haematogenous miliary and slightly larger lesions, casts of smaller bronchioles and diffuse emphysema. In short, the lungs showed a mixture of both haematogenous and bronchogenic lesions, and it is most likely that the apical ulcerations arose from antecedent vascular foci. The caseous nodes in the abdomen may have been the source for the lympho-haematogenous spread.

SUMMARY

Tuberculosis is very often a systemic disease. Pulmonary tuberculosis may develop by exogenous and endogenous reinfection. Regardless of their derivation, the lesions may regress or progress. If the latter takes place in a case of original haematogenous pulmonary tuberculosis, a superimposed picture of bronchogenic phthisis will take place which may obscure its endogenous genesis. This sequence of events is a more frequent source of "adult phthisis" than has been generally recognized

hitherto. The term "transitional forms" has been used by Grethmann and Miller to describe these cases.

The evolution of haematogenous pulmonary tuberculosis into bronchogenic tuberculosis is briefly reviewed from pathological, roentgenological and clinical points of view. Four cases have been presented to demonstrate this transition especially by serial roentgenograms.

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NONTUBERCULOUS UPPER LOBE BRONCHIECTASIS[1]

A Report of Three Cases

A. B. RILANCE AND KIRBY S. HOWLETT, JR.

Bronchiectasis of nontuberculous origin confined wholly, or even in major degree, to an upper lobe of the lung is apparently an uncommon lesion. In 1916 McCrae and Funk (1) reported one case in which this diagnosis was made clinically and confirmed at autopsy. Prior to coming under their observation this patient had been treated in three tuberculosis sanatoria, with a diagnosis of advanced pulmonary tuberculosis in each. McCrae and Funk stressed the fact that the problem of diagnosis of upper lobe bronchiectasis is largely one of differentiation from pulmonary tuberculosis. Nevertheless, a survey of a number of cases reported since 1916 reveals no feature more striking than the almost unrelieved regularity with which pulmonary tuberculosis had been the first diagnosis received by the patient. Many of them had needlessly spent years in tuberculosis sanatoria before the correct diagnosis was established. The patient with extensive bilateral upper lobe bronchiectasis reported by Steidl and Heise (2) is an example, having spent many years of chronic illness in the futile search for a cure of supposed pulmonary tuberculosis before admission to the Trudeau Sanatorium.

Rubin and Newman (3) have reported 11 cases of upper lobe bronchiectasis and noted 16 additional cases collected from other reports. In 3 of their cases the bronchiectasis was definitely secondary to chronic pulmonary tuberculosis, however, and the authors believed that the majority of their other cases showed good evidence that a healed tuberculosis had been the causative factor. In 6 of their cases the specific elements of tuberculosis were, nevertheless, lacking at autopsy, and these authors, also, emphasized the importance of a clinical differentiation between bronchiectasis of the upper lobe and pulmonary tuberculosis. Their findings will be considered further in the discussion which follows our own case reports.

Graham (4) reports a series of 149 cases of bronchiectasis from the

[1] From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.

Barnes Hospital among which there was one case of isolated nontuberculous upper lobe involvement. Churchill (5) reports that, of 85 lobectomies for bronchiectasis, only 2 were for disease confined to an upper lobe. In one of these the lesion was a localized bronchiectatic cyst of the left upper lobe rather than the classical cylindrical or saccular disease. In his other case there was true saccular bronchiectasis of the right upper lobe. Lobectomy was performed in both these instances and tuberculosis was ruled out on pathological examination.

During the past three years a diagnosis of nontuberculous bronchiectasis of the right upper lobe has been made in 3 patients admitted to the Laurel Heights Sanatorium. Prior to admission, a presumptive diagnosis of pulmonary tuberculosis had been made in each of these cases by the referring physician.

CASE REPORTS

Case 1: No. 5777. T. B., a white, single, 40 year old woman, was admitted to Laurel Heights on May 22, 1931, complaining of cough and expectoration. Her mother had died of pulmonary tuberculosis in 1900. Since the age of fifteen years, she had noted frequent chest colds with much cough and expectoration. Her general health, also, had been under par since an early age. She had had a right sided pneumonia in 1923 and was ill for two and one-half weeks at that time. In 1924 she noticed loss of appetite, copious sputum and loss of weight. She was seen by a physician and was sent to a tuberculosis sanatorium for treatment. A diagnosis of tuberculosis was never definitely substantiated there because, in spite of abundant mucopurulent expectoration, tubercle bacilli were never found. X-ray at that time showed definite infiltration in the right upper lobe, felt to be suggestive of bronchiectasis. General improvement was noticed under sanatorium care, and the patient was discharged as improved in April, 1926, eighteen months after admission. Abundant expectoration was continuous during all this period of treatment. Following discharge she felt fairly well in spite of persistent cough and expectoration until her admission here in 1931. Upper respiratory infections were regularly accompanied by an increase of pulmonary symptoms, which gradually subsided to their former level with the subsidence of the upper respiratory infection.

On admission she was found to be 35 pounds under her standard weight. Cough and expectoration were marked. Examination of the chest revealed bronchovesicular breathing and many coarse and moderately coarse râles above the fourth rib and fifth vertebral spine on the right side. The left lung was normal. The fingers showed mild clubbing. Under treatment she failed to show any definite improvement. Cough and copious mucopurulent sputum

persisted. The sputum at all times was negative for tubercle bacilli both by direct smear and concentration methods.

An X-ray film on admission, May 26, 1931, revealed no abnormality in the left lung. Extending out from the hilum on the right side into the upper and middle thirds of the lung field was a reticulated, honeycombed fibrosis, very suggestive of bronchiectasis. Serial X-ray films showed relatively little change over a period of four years. At various intervals, however, temporary increases of collateral reaction were noted. These were interpreted as evidence of increased pneumonitis, and were usually associated with increase in respiratory symptoms and low grade fever. X-ray films following discharge, February 28, 1936, (figure 1) were taken during one of these episodes, and a well outlined bronchiectatic cavity with definite fluid level can be seen at the level of the first interspace on the right side. X-ray films taken after lipiodol filling of the bronchi, April 10, 1935, (figure 2) revealed considerable puddling in saccular dilatations in the branches of the right upper lobe bronchus. At a later date, lipiodol filling of the right middle and lower lobes and of the left lung showed essentially normal conditions. A final diagnosis of nontuberculous bronchiectasis of the right upper lobe was made. The patient was discharged on October 13, 1935.

Since discharge the patient's status has changed little. Her general health has remained fairly good but cough and expectoration have persisted unchanged, being somewhat variable with the seasons of the year, and increasing temporarily whenever an acute upper respiratory infection occurs. She has led what has long been for her a normal life, with obvious handicaps produced by the persistent pulmonary symptoms. X-ray, also, has shown no essential change, except for the slight variation at times in the amount of pneumonitis and retained secretions in the involved lobe. This patient has been seen by a thoracic surgeon, and the question of lobectomy was seriously considered. Although this was regarded as a highly desirable form of treatment for her type of disease, a final decision against lobectomy was made since it was felt that the patient's age and almost a lifetime of impaired health made her a poor operative risk. In the summer of 1938, she received a course of deep X-ray therapy over the involved lobe. This has, as yet, produced no improvement, and her status, both clinically and by X-ray, remains the same as at discharge.

Case 2: No. 6954. G. S., a white male, age 20, was admitted to Laurel Heights on April 5, 1936, complaining of slight expectoration. The family history was negative for tuberculosis. There was no past history of significant pulmonary symptoms. Approximately nine years prior to admission, while riding a bicycle, the patient had had a sudden haemoptysis of several ounces. This occurred at the age of eleven years. The patient was in excellent general

health at the time, and the blood spitting occurred without any premonitory symptoms whatsoever. There was no subsequent impairment of the patient's health, and no further pulmonary symptoms occurred until 1931, more than four years later. In 1931, four and one-half years prior to admission, the patient had a series of haemoptyses and raised large quantities of blood over a period of four days. Prior to that time he had been in good health and he continued so following the haemoptyses. One and one-half years later (1933) he had another severe haemoptysis. A roentgenogram of the chest was made at that time and the patient was followed at a tuberculosis dispensary for a time. He continued to be well with no sputum until the winter of 1935, five months prior to his admission, when he had another series of haemoptyses, intermittent for a period of seven days. At this time he was raising blood in "mouthfuls." Following another X-ray film he was advised to enter a sanatorium. Two months prior to admission he noticed a little sputum for the first time. There was occasional pain in the right chest. During this interval he was studied in a general hospital. He reported that 27 sputum examinations had been made there, and that, of these, one (the 23rd) was reported positive for tubercle bacilli.

On admission his weight was 195 pounds, 39 pounds over his standard weight. His general condition was excellent. Examination of the lungs revealed diminished breath sounds above the third rib and fifth vertebral spine with fine and moderately coarse râles above the clavicle on the right side.

An X-ray film, April 6, 1936, (figure 3) revealed infiltration to the third rib on the right, consisting of fine linear strands of fibrosis with a suggestive reticular appearance. The sputum was small in quantity and numerous specimens were consistently negative for tubercle bacilli by direct smear, concentration methods, culture and guinea pig inoculation. The tuberculin test was positive with .000,02 mg. of PPD. A bronchogram, June 27, 1936, (figure 4) revealed gross bronchial dilatation in the right upper lobe with puddling particularly in the first anterior interspace. The bronchi of the remaining lobes filled normally. The patient was discharged on June 30, 1936 with a diagnosis of nontuberculous right upper lobe bronchiectasis of the "dry" type. In view of all the evidence against a diagnosis of pulmonary tuberculosis, to be discussed later, we felt justified in refusing to make such a diagnosis on the basis of the single positive sputum report from the outside hospital, especially since 26 other examinations at the same hospital were all negative.

Soon after discharge the patient resumed work as manager of a telegraph office. On June 12, 1937, he had a haemoptysis of ten to twenty ounces of blood. He continued to expectorate smaller quantities of blood for three days, though he felt, otherwise, perfectly well. X-ray film of June 15, 1937 revealed increased haziness in the area previously demonstrated to contain bronchiectasis. An X-ray film made three weeks later, July 6, 1937, revealed complete

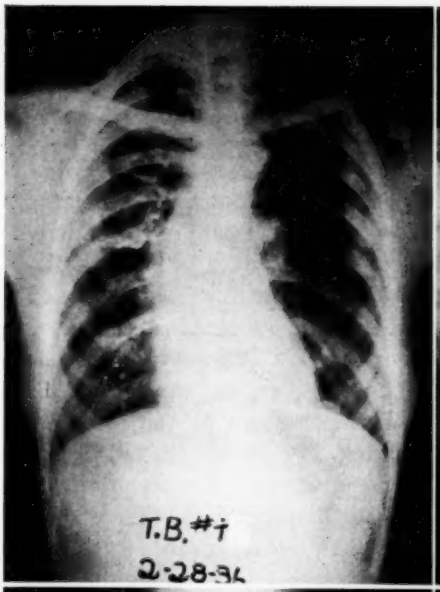

FIG. 1

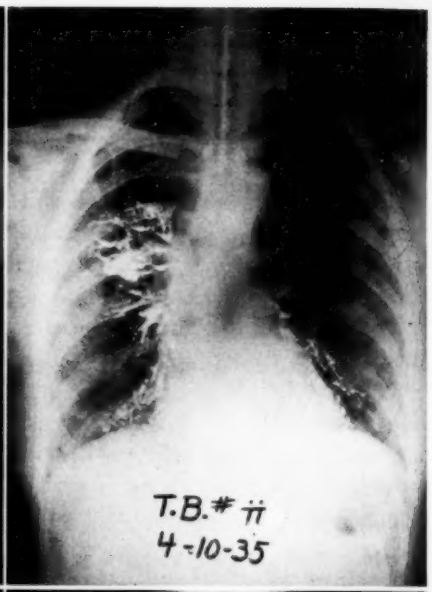

FIG. 2

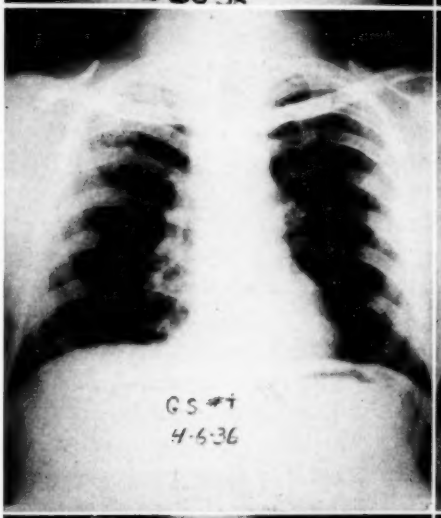

FIG. 3

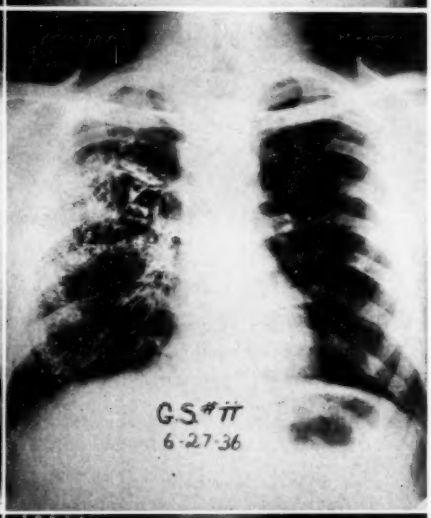

FIG. 4

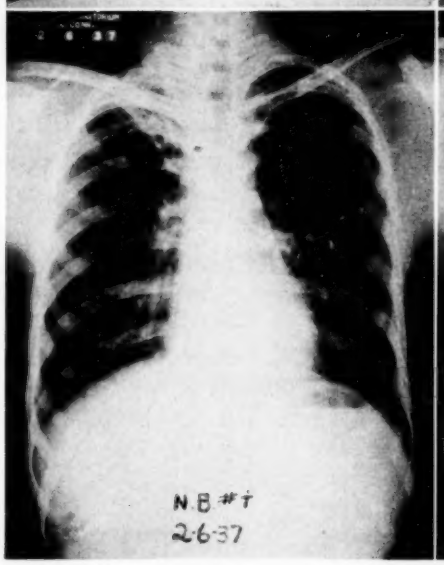

FIG. 5

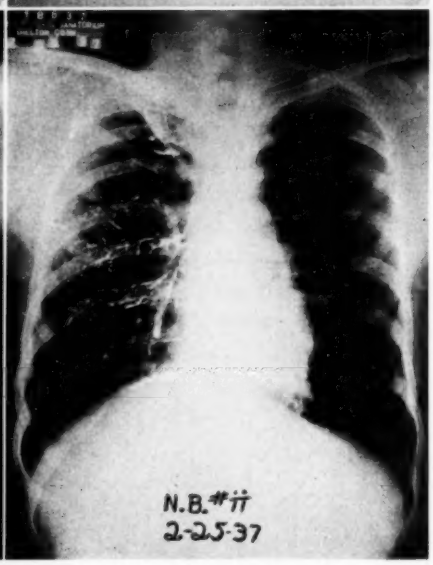

FIG. 6

FIGS. 1–6

clearing of this haziness and restoration of the lung to its former appearance. His general health remained quite unimpaired and no pulmonary symptoms followed the episode of blood spitting. We learned later that he had returned to work as soon as his blood spitting subsided.

Except for this episode, the patient has remained perfectly well ever since discharge. Moreover, cough has virtually ceased and there is now only a minimum amount of mucoid sputum each morning. A recent examination of the chest was negative except for impaired resonance and few transient moderately coarse râles above the level of the clavicle and third vertebral spine on the right. He has worked without interruption except for the very brief interval of four days in 1937.

The question of lobectomy has been discussed with this patient since, in spite of his favorable course so far, we feel that the outlook for the future is extremely uncertain. In the absence of increasing symptoms or other evidence of progressive pathology we have acceded to the patient's wish to defer decision on this point for the present.

Case 3: No. 7148. N. B., a white male, age 29, was admitted on February 5, 1937 complaining of slight cough and expectoration. The family history was negative for tuberculosis. In childhood he had measles, mumps and whooping cough. He had pneumonia at the age of one and "rheumatism" at the age of two. There was a tonsillectomy at twelve. He suffered a mild attack of influenza in 1933. While onset was indefinite, he felt that he had been somewhat short of breath for five or six years. In June, 1936, he first noticed malaise, anorexia and increased dyspnoea. He lost 6 pounds in weight. In July, 1936 he developed a moderate cough with slight expectoration. During

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FIG. 1. Case 1. February 28, 1936. Plain roentgenogram showing reticulated honeycombed fibrosis in right upper lobe. Remainder of pulmonic fields normal. Bronchiectatic cavity with fluid level is visible at level of first anterior intercostal space.

FIG. 2. Case 1. April 10, 1935. Roentgenogram following instillation of lipiodol. Puddling of lipiodol in bronchial dilatations of branches of right upper lobe bronchus is visible.

FIG. 3. Case 2. April 6, 1936. Plain roentgenogram showing fine linear strands suggesting reticulated fibrosis in right upper lobe (above level of anterior third rib).

FIG. 4. Case 2. June 27, 1936. Roentgenogram following instillation of lipiodol. Gross dilatation of branches of right upper lobe bronchus is visible.

FIG. 5. Case 3. February 6, 1937. Plain roentgenogram showing retracted and fibrotic upper lobe with thin-walled annular shadows bordering this lesion below (at level of anterior second rib).

FIG. 6. Case 3. February 25, 1937. Roentgenogram following instillation of lipiodol. Distribution of the right upper lobe bronchus is shown to be confined to the triangular area of fibrosis extending into extreme apex. Puddling of lipiodol in dilated bronchi is visible in this area, and one well defined cyst-like cavity is outlined at its lower margin.

a severe coughing spell he expectorated one dram of blood. Three specimens of sputum examined by his physician were negative for tubercle bacilli.

On admission he was 27 pounds under his standard weight but only 5 pounds under his best previous weight. His general condition was good. Examination of the chest revealed on the right impaired resonance above the second rib and fifth vertebral spine, whispered pectoriloquy above the second rib and fourth vertebral spine, and a few fine râles above the second rib and fifth vertebral spine. The left lung was normal.

X-ray film of February 6, 1937 (figure 5) showed a sharply demarcated dense shadow running from the right hilum to the extreme apex with peculiar thin-walled annular shadows bordering it below. The appearance suggested an atelectasis of the upper lobe, while the adjacent shadows had the appearance of cystic bronchial dilatations or, possibly, thin-walled emphysematous blebs. A small amount of mucopurulent sputum was consistently negative for tubercle bacilli, by direct and concentration methods and by culture. The tuberculin test was positive with .000,02 mg. of PPD.

X-ray films (figure 6) after filling the right upper lobe bronchus with lipiodol revealed bronchial dilatation and much puddling of lipiodol in the extreme apex with one well filled cyst-like cavity. The lipiodol had obviously reached this cyst-like cavity by way of the right upper lobe bronchus. The three lobes of the right lung could be readily identified after their bronchi had been outlined with lipiodol. The upper lobe could be demonstrated to be shrunken into the extreme apex of the right hemithorax. The middle and lower lobes filled all the space in the right hemithorax below the second anterior rib. The patient was given a diagnosis of nontuberculous bronchiectasis of the right upper lobe with atelectasis. He was discharged on February 5, 1937 in good general condition.

After discharge this patient returned to a relatively normal life and his course since discharge has been uneventful. His general condition and symptoms remain unchanged, with persistence of dyspnoea, mild cough and a small amount of mucopurulent sputum. Haemoptysis has not recurred. His lesion has shown no change by X-ray. The presence of dyspnoea, and the mild nature of the patient's catarrhal and general symptoms make us feel that surgical treatment is not advisable in this case.

DISCUSSION

In the effort to encourage the earlier and more frequent diagnosis of pulmonary tuberculosis, where it exists, many writers have rightly emphasized the presumably tuberculous nature of parenchymatous X-ray lesions in the upper one-third of the lungs, and of haemoptyses unexplained on another basis. When either of these findings, or both, occur

in a patient whose general health is impaired, or who also presents symptoms of chronic cough and expectoration, the presumption of pulmonary tuberculosis is, indeed, strong.

Nevertheless, the possibility of a nontuberculous aetiology must always be considered, and another cause must be sought with special persistence when there are good reasons for doubting a tuberculous basis for such findings. Because of its rarity, nontuberculous bronchiectasis of the upper lobe is particularly likely to escape consideration in the differential diagnosis. Since the treatment of choice for bronchiectasis is entirely different from that for tuberculosis, the practical importance of such a differentiation is obvious. Even the cases of bronchiectasis unsuitable for lobectomy may at least be spared the futile expenditure of time and money which the unsuccessful treatment of a supposed tuberculosis entails. The futility of such treatment in these patients is well illustrated in our first case and in the majority of the cases reported by other authors.

Since each of the 3 cases reported was sent into the sanatorium with a presumptive diagnosis of pulmonary tuberculosis, the first diagnostic problem was one of exclusion. There was, in each case, good reason, from both clinical and X-ray standpoints, to seriously doubt the presence of pulmonary tuberculosis. Without going further into the details of diagnostic reasoning in each case, the following points may be enumerated as ones which we consider especially significant. The specific cases to which they apply are noted in parantheses.

1. While the presence of a positive sputum is by no means necessary for the diagnosis of pulmonary tuberculosis, the persistence, as a major symptom, of abundant expectoration of mucopurulent sputum which has never been positive for tubercle bacilli occurs rarely indeed in patients with uncomplicated tuberculosis, and is a strong indication for a search for other causes (case 1).

2. The presence of tuberculous pulmonary cavities, as revealed by the X-ray, is practically always associated with a positive sputum when good sputum specimens are obtainable, and when thorough methods of sputum examination are employed. The absence of a positive sputum under such circumstances is strong evidence that annular pulmonary shadows seen in the roentgenogram have another pathological basis (cases 1 and 3).

3. Large haemoptyses may be the first symptoms of pulmonary tuberculosis recognized by the patient as significant. If produced by tuber-

culosis, however, large haemoptyses are extremely likely to be associated with, or followed by, at least some impairment of general health. Moreover, roentgenological and clinical evidence of some progression of disease is rarely lacking, especially when the haemoptyses are recurrent. The recurrence of large haemoptyses out of a clear sky, and without any of the associated phenomena just mentioned, is decidedly not characteristic of pulmonary tuberculosis. Haemoptysis is, moreover, an extremely common symptom of bronchiectasis (case 2).

4. The symptoms presented by each of the cases reported would, if due to pulmonary tuberculosis, be indicative of a definitely active lesion. It is extremely unlikely that an active tuberculous lesion would remain essentially stationary over a period of time as long as these patients have been observed, when the normal activity of the patients was not greatly restricted. This point is of significance in confirming the nontuberculous nature of their disease (cases 1, 2, and 3).

Space and emphasis have been given the above points because the tendency to regard these patients as tuberculous is the chief obstacle to a correct diagnosis. Once the physician has directed his attention away from tuberculosis the diagnosis presents little difficulty.

5. While roentgenographic features have been mentioned in connection with some of the clinical points just discussed, the appearance of the lesion on the plain roentgenogram was sufficient in all three cases to cast serious doubt upon a diagnosis of pulmonary tuberculosis. While the appearance of the lesion was different in each case, in all three cases the characteristic appearances of pulmonary tuberculosis were lacking. Moreover, the lesions presented in common a peculiar reticulated appearance, and in cases 1 and 3 there were also noted the very thin-walled cavities previously described. These features were considered highly suggestive of bronchiectasis rather than of pulmonary tuberculosis.

Finally, of course, the filling of the bronchi of the involved lobe with lipiodol served to demonstrate definitely the bronchiectatic involvement in each case. Contrary to the opinion expressed by Rubin and Newman (3), we believe that this procedure is essential to a positive and complete diagnosis, no matter how strong the presumption of bronchiectasis may be on grounds of clinical features, physical findings and the plain roentgenogram.

It should be pointed out that bronchiectasis of an upper lobe is by no means a rare finding in association with tuberculous involvement of

the lobe. The three definitely tuberculous cases reported by Rubin and Newman (3) have already been mentioned, and these authors believe that bronchiectasis of the upper lobe is, in the majority of instances, the result of a healed tuberculosis. It is, however, noteworthy that 6 of their other cases showed no evidence of tuberculosis except fibrosis, even on pathological examination. Rilance will report elsewhere a number of cases of pulmonary tuberculosis in which, with lipiodol, bronchiectasis was demonstrated in association with both active and healed tuberculous lesions, and many of these patients presented definite clinical features of both diseases. Some degree of bronchial dilatation is certainly extremely common in chronic fibroid phthisis, and the bronchiectatic involvement may dominate the clinical picture entirely when the tuberculosis is healed. We agree, therefore, that either an active or a healed tuberculosis is the causative factor in the vast majority of cases of bronchiectasis of the upper lobe, if all cases with demonstrable bronchiectasis in this location are included. It is, moreover, particularly important that, in the patients with healed tuberculosis, the secondary bronchiectasis be recognized as the source of symptoms, in order that sanatorium treatment may not be needlessly prolonged. In the cases observed at the Laurel Heights Sanatorium, however, with both lesions intimately associated, the evidences of the fundamentally tuberculous nature of their disease were abundant.

In contradistinction to the tuberculous cases just mentioned, the 3 cases presented here present findings entirely compatible with bronchiectasis alone, with the same uncertainty as to primary aetiology which so often exists in bronchiectasis of the middle and lower lobes. In fact cases 1 and 2 present histories especially characteristic of bronchiectasis, one of the conventional "wet" type, the other of the less common "dry" type of the disease. We believe that adequate reasons have been given for excluding clinical tuberculosis as a factor in these 3 cases, even though pathological examination of tissue, which confirmed the absence of tuberculosis in the 2 cases of Churchill (5), has not been possible.

It should, perhaps, also be mentioned, as a matter of collateral interest, that the lingula on the left does not share in the relative freedom of the upper lobes from bronchiectasis. Churchill (5) states that the lingula was also involved in at least 80 per cent of cases of left lower lobe bronchiectasis seen by him.

SUMMARY

1. Three[2] cases of bronchiectasis of the right upper lobe are reported.

2. The upper lobe is a rare site of nontuberculous bronchiectasis and the symptoms simulate, in many respects, the symptoms of pulmonary tuberculosis, which is frequent in this location. Hence the physician must be on guard against an erroneous diagnosis of pulmonary tuberculosis in such cases.

3. Factors leading to the exclusion of pulmonary tuberculosis and other factors involved in the differential diagnosis are discussed.

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[2] Since this paper has been written, a fourth case has come to our attention which we believe conforms to the criteria necessary for a diagnosis of nontuberculous upper lobe bronchiectasis. However, the period of observation has been too short to warrant inclusion in this paper.

CALCIFICATION OF THE PLEURA[1]

CLEAVELAND FLOYD AND ROBERT H. HEPBURN

Pleural calcification, or *pleura petrificans*, is a pathological entity first described by Morgagni (1682–1771). Little attention has been paid to the condition until within the last thirty-five years, since when reports of about one hundred and fifty cases have appeared in medical literature. Prior to 1922 almost all cases were embodied in postmortem reports, but since that date increasing clinical data have accumulated, elicited by X-ray observations. Little has been added in recent years to the knowledge of the pathology of this condition, but its physico-chemical aspects have been subject to extensive investigation.

At the present time, the application of thoracic surgery in its various forms to many chest conditions has created a renewed interest in pathological conditions not only of the lung, but of the pleura, and among these is pleural calcification.

In the consideration of the subject the investigator is at once confronted with the fact of its infrequency as noted by pathologists and clinicians. The occurrence of pleural effusion and empyema as an antecedent of this condition commonly appears in every series reported. Pleural infections are observed yearly by the thousands and yet calcification, as a sequel, is relatively rare. Ulrich reports that Kohn found 0.87 per cent among 1,845 X-ray examinations, and at the Greifswalder Medizinische Klinik in 4,500 pulmonary examinations only 8 cases of calcification were found, or 0.18 per cent. In our own studies during a period of ten years, in which more than 15,000 roentgenological chest examinations have been made, the condition has been found 28 times.

The predisposing causes of pleural calosities are:

(a) Actinomycosis
(b) Empyema
(c) Pleurisy with effusion
(d) Tuberculosis
(e) Trauma

[1] From the Division of Tuberculosis, Boston Health Department, Boston, Massachusetts.

Kraus, Munster and Baumeister have reported the unusual findings of actinomycosis involving the pleural cavity. These infections are probably secondary to abdominal disease, and are of long duration, and are accompanied by great destruction of tissue.

The occurrence of calcification following empyema has occasionally been noted to follow an acute infection. In most instances a history only has been obtained of this lesion, antedating by many years the discovery of the deposit of calcium in the chest, and its close relationship probably only occurs where such cases have not received adequate drainage and there has been retention of products of inflammation with organization and later deposition of calcium salts.

One of the more prevalent conditions antedating pleural calcification is that of pleurisy, generally of an extensive and severe grade, often with the history of accompanying effusion. Here again almost all the cases have been seen only at the time of the terminal condition and have not been followed from the initial infection until the pleura is impregnated with calcium.

Many of these cases of pleural infection may be due to tuberculosis but this, as a cause leading to calcification, is not preëminent even in clinics devoted primarily to its study. In our own series, where chronic chest conditions make up the great bulk of cases under observation, not more than one-fourth of those where this condition is present show signs of old pulmonary lesions.

Injury to the lung from gun-shot wounds, or to the pleura following trauma of the chest, gives rise to about 40 per cent of the cases of pleural calcification (Behrendt). This has been especially true since the World War.

The great majority of cases of pleural calcification have been found in middle or later life. The explanation of this fact is that it probably requires months or years to establish a demonstrable lesion of this nature, although there are on record a few cases in which the process was noted to have arisen within a few months. Lippmann reports a case following pneumonia which was detected four months after the acute process had taken place, and Brauer reports two cases in childhood: the first showed a heavy area of calcification over the lung and left diaphragm six years after the occurrence of pleurisy with effusion; the second occurred in a child of twelve and one-half years following pleurisy at the age of eighteen months. X-ray films showed a heavy chalky shadow in the chest.

It is not uncommon to see calcification occur in the hilar lymph nodes

following a tuberculous infection after an interval of twelve to eighteen months, but this process in the pleura, in most instances, requires a much longer period of time. It should not be forgotten, however, that pleural calcification gives rise to few symptoms, and the detection of the condition generally follows routine examinations or is found at autopsy.

In no case have we seen the building up of calcium in the pleura even where the condition has been under observation for a number of years. In all the cases here reported the process appears to be a terminal one and to have come to an end when first detected.

Aside from the infiltration of calcium into the pleura, Endres notes the rare occurrence of calcium stones lying in the pleural cavity. With the not infrequent occurrence of fibrin bodies in the pleural cavity, secondary to the induction of artificial pneumothorax, it is not inconceivable that this pathological rarity may be much more frequently noted in the future.

The biochemical processes involved in pleural calcification have elicited much investigation. Aschoff speaks of blood albumen autolytically demolished as acting to "seize lime from the blood." The large percentage of cases in which trauma and pleural calcification are associated has led to the belief that the presence of haemosiderin must exert some attraction for the lime salts of the blood. The presence of a calcium diathesis in these cases has been considered, but not proved or generally accepted.

Pritchard believes that certain steps are necessary before the deposition of calcium salts occurs. First, a lowered tissue vitality following injury or infection, with the resulting impaired circulation in the part, followed by fibrosis, which later shows hyalin degeneration and into which calcium salts are deposited. Forscher and Seelijer believe that there is a change in hydrogen ion concentration and the existence of phosphoric-acid splitting enzymes in such pleural lesions that later show the presence of calcification. Oldenberg thinks the primary steps in the process are due to the lowering of carbonic potential in the blood serum and the ratio of tricalcium phosphate and calcium carbonate in the blood serum.

Wells, from a very considerable number of experimental observations upon calcified tissue, makes the following observations:

The essential difference between calcification and ossification is chiefly morphological. Calcification is deposited in dead tissue, or in tissue of low vitality in the form of inorganic salts; first granular, then by fusion forming masses of

homogeneity, not necessarily permanent, as in calcification in the kidney which may be reabsorbed in a few weeks (Von Weera).

Ossification of calcium deposits is related to living cells which determine the form of deposition, which may dissolve in organic salts causing their deposition as is necessary; otherwise, the two processes are the same. In mammals, the proportions of calcium phosphate and of calcium carbonate are the same as in bone,—that is 85 per cent to 95 per cent calcium phosphate—10 per cent to 15 per cent calcium carbonate. Pathological calcification not infrequently undergoes metamorphosis into true bone, examples being bone formation in the eye and lymph nodes. According to Poscharisky 60 per cent of 17 calcified nodes showed true bone formation. Leik produced bone formation constantly in the pelvis of rabbits' kidneys after tying the renal artery, in 20 days, provided he had collateral circulation.

Calcium salts exert specific influence on connective tissue cells which causes them to take on active growth and undergo metaplasia into osteoblasts and bone corpuscles.

In the normal formation of bone we get first, deposit of calcium salts, second, increased vascularity with new cells forcing their way into calcified tissue, and then the appearance of osteoblasts and bone corpuscles. The precipitation of calcium salts may be made possible by increased alkalization of the degenerating tissues which might cause mono- and dicalcium phosphates and bicarbonate of calcium to be converted into the less soluble basic salts and precipitate from the blood. A change in reaction may be sufficient to cause precipitation of calcium salts in the blood in normal tissues, as occurs in metastatic calcification.

Wells states that we have the following facts, upon which to base consideration in determining the chemical changes that take place in the production of pathological calcification: Calcium salts are held in solution or in suspension by the proteins in the blood either as carbonate and phosphate themselves, or as calcium-ion-protein compounds. This suspension is an unstable condition and is capable of being overthrown by increased alkalinity of the blood, changes in proteins of carbon dioxide content or changes in the quantity or the composition of the calcium salts. Retrogressive change in tissues, especially where hyalin degeneration or necrosis occurs, is a very favorable condition. Increased alkalinity or decreased carbon dioxide in the degenerating tissues causes precipitation of the inorganic salts in the fluids seeping through such areas.

Although the clinical manifestations of calcium deposition in the pleura are almost negligible, the pulmonary capacity may be limited causing

some dyspnoea upon exertion. A sense of weight or heaviness may occur on the affected side if the lesion is of any extent. Ordinarily the process has been built up so gradually that the individual is not aware of its presence. On examination the chest shows marked flattening and frequently narrowing of Krönig's isthmus. There is marked lagging on full respiration and the mobility of the diaphragm is restricted. The percussion note is flat and the chest wall lacks elasticity. Tactile fremitus is greatly diminished or entirely absent. Auscultation shows a distant respiratory murmur, and voice sounds are poorly transmitted. The clinical signs suggest the presence of pleural thickening.

Gardy and Baize have investigated a number of their reported cases with a thoracocentesis needle, and they have noted the resistance encountered by it as it passes into the pleural cavity, "striking a hard obstacle of crustaceous consistency."

The X-ray shadows cast by the plaques of calcium appear in various ways. There are often small, granular or bead-like masses, confined to one small portion of the pleura. At other times the process may be entirely limited to the costophrenic angle in which an opaque mass may exist. In instances where the process is more extensive a broad band extending from the axilla to the spine may girdle a large portion of the lung. Not uncommonly as a part of this deposit are spicules of calcium extending into the interlobar fissures or into the lung substance itself. These projections may be fairly numerous and of such striking appearance that they have been described as stalactites of calcium (case 1). Less commonly the apex of the lung may be enclosed in a dense cap of bone-like tissue. Where the lesion has been produced in the upper portion of the chest, marked retraction of the lung substance is seen on the X-ray plate, and even on full inspiration there remains an unoccupied pleural space between the calcium load and the parietal pleura (cases 2 and 3). Where this condition is the end result of an old pleural lesion one would expect to find its appearance most marked in the lower portion of the chest. This is often the case (case 4). In those instances where the lung shows marked retraction, the calcium sheet has been found adherent to the visceral pleura (case 5). In one instance, it was firmly adherent to the parietal wall, rather than the visceral pleura. It is noteworthy that, in cases in which pulmonary tuberculosis has been found to be present coincident with the deposit of calcium in the pleura, they rarely are found involving those portions of the lung and pleura that are in apposition. The reason for this is probably due to

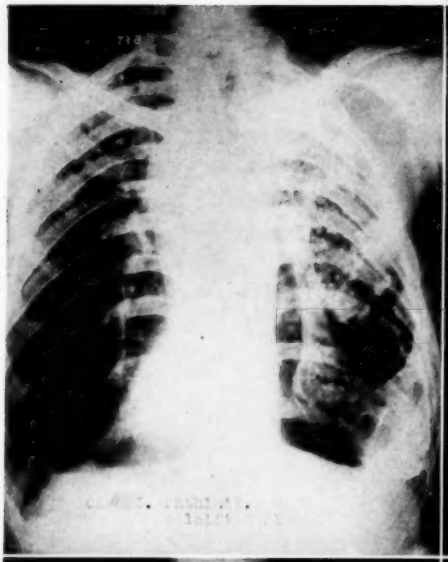

FIG. 1

FIG. 2

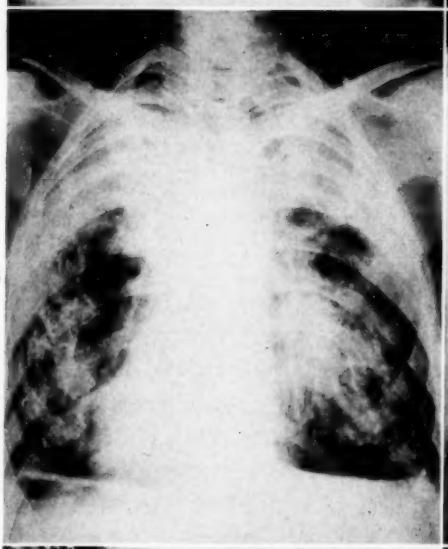

FIG. 3

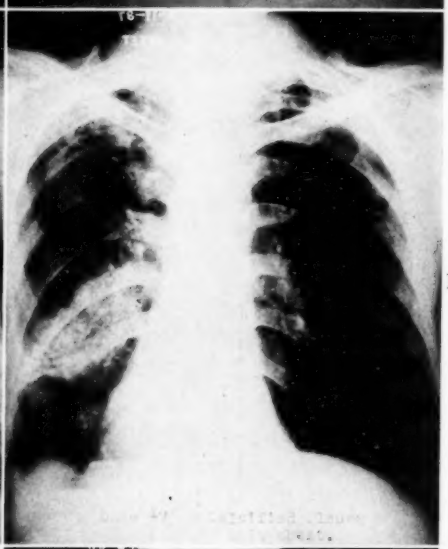

FIG. 4

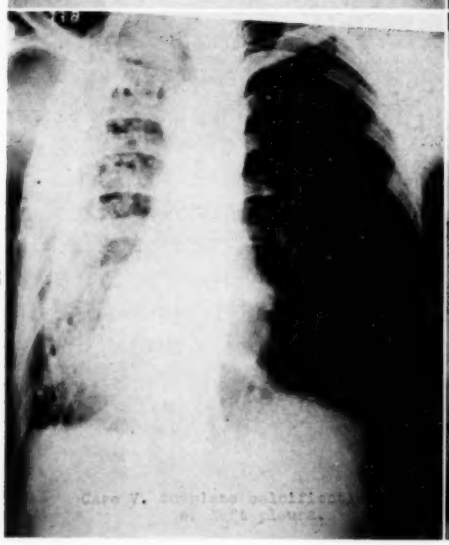

FIG. 5

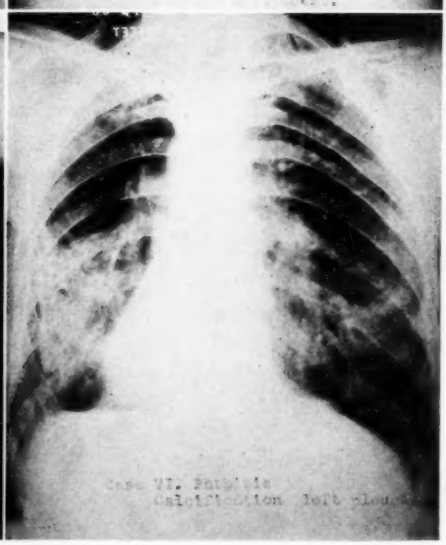

FIG. 6

FIGS. 1–6

the fact that caseation of the pleura concomitant with that of the lung is of very infrequent occurrence. Furthermore, the albuminous elements in chronic pleural disease, unless encapsulated, are likely to gravitate to the lower portion of the chest, and this is where the calcium masses are most commonly found. Rarely the process may be bilateral (case 6).

PATHOLOGICAL STRUCTURE OF CALCIFIED PLEURA

The autopsy records of the Boston City Hospital contain few reports of calcified pleura. The pathological picture presented in these cases may be summarized as follows: Encasing a portion of the lung, more commonly toward the base and over the diaphragmatic surface, but occasionally seen forming a hood of the upper lobe of the lung, is a false membrane, made up of tough fibrous tissue irregular in density and outline. This membrane may follow the contour of the lung, extending into the interlobular fissures and not uncommonly involving the costophrenic sinus. Upon section, the material may appear as dense cartilaginous tissue, and here and there in it are found irregular areas of calcification in the form of plaques with rough edges, bands extending around the lung surface and even advancing into the lung itself as spinous processes. These areas of calcification vary in thickness and appear to have risen from a deposition of calcium salts not only into the superimposed fibrous membrane covering the lung, but apparently also extending outward into the mass of inflammatory exudate. The calcium shell is of bony hardness in many instances, but where the thickness is of limited extent it may crumble under the fingers.

In one autopsy which we observed, the right pleural cavity was obliterated by dense fibrous tissue and the parietal pleura was calcified over an area 21 by 17 cm. between the seventh and the eleventh ribs. One portion of this hard shell was 2 cm. in diameter and was elevated at least 1 cm. above the surrounding calcified pleura.

Histological examination of this material showed it to be free of bone corpuscles or any evidence of Haversian canals, thus indicating the lack of bony structure.

FIG. 1. Case 1. Phthisis. Calcified pleura
FIG. 2. Case 2. Calcified pleura right chest
FIG. 3. Case 3. Bilateral calcified pleura
FIG. 4. Case 4. Calcified pleura left chest
FIG. 5. Case 5. Complete calcification of left pleura
FIG. 6. Case 6. Phthisis. Calcification left pleura

Tuffier and Jardy decalcified calcified plaques in autopsies reported by them. This material was found to be made up of a homogeneous mass with little cellular structure containing no nuclei. These observations corroborate those by Wells and others who believe that hyalin degeneration of fibrous tissue precedes the deposition of calcium salts.

The rôle of tuberculosis in calcified pleura: There is considerable difference of opinion as to the part played by pulmonary tuberculosis in the calcification of the pleura. Some observers, notably Ulrich, believe that tuberculosis has only a limited aetiological significance, while Engel and Schall believe that tuberculous pleurisy plays a significant part in cases where calcification later develops in the pleural cavity. In most reports appearing in the literature, some mention is made of the relationship between tuberculosis of the pleura and its later calcification. In all the cases observed in this study this condition was either present in active form, or the past history suggested its former occurrence. In one case, it is of interest to note that three factors may have played a part in the final condition of the pleura, namely, gun-shot wounds, empyema and tuberculosis.

CONCLUSIONS

The deposition of calcium in the pleural cavity is a pathological entity occurring following bleeding into the chest cavity, in certain instances of severe empyema and pleural effusion, and in tuberculosis, either giving rise to phthisis or a tuberculous effusion.

The condition occurs where there has been extensive tissue damage, following which the connective tissue repair has shown hyalin degeneration followed by the deposition of calcium salts. The end result may be localized in any portion of the chest, producing a marked retraction of the pulmonary parenchyma if the upper lobes are involved and giving rise to clinical symptoms where vital capacity is sufficiently reduced. The diagnosis may be suspected upon the use of the exploratory needle, but its actual presence and extent will be proved by the roentgen film in life, or at autopsy. With the extensive use of artificial pneumothorax in the treatment of pulmonary tuberculosis and the occurrence of empyema as a complication, this condition may well be of greater clinical importance in the future than it has been in the past.

We wish to express our appreciation to Dr. F. B. Mallory for the use of the pathological material of the Boston City Hospital.

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CLINICAL AND LABORATORY NOTES

SARCOMA OF THE LUNG[1,2]

W. DEAN STEWARD

Omitting lymphosarcoma, primary sarcoma of the lung is among the rarer pathological lesions. Because of this, it was thought that a case report on such a subject should be of interest.

The history of this case, as obtained from the patient, was not considered very reliable. With the aid of data obtained from the child's family physicians, it is believed that the history given here is essentially correct.

M. S., no. 4991, an adopted child of 12 years of age, was admitted to Pine Breeze Sanatorium on July 29, 1938, with the chief complaint of cough, weight loss and pulmonary haemorrhage. The family history was negative according to the reports.

She was born prematurely (seven and a half months) and was never very robust. At the age of six she had measles complicated by severe bronchopneumonia; recovery was by lysis. In December, 1937 she was examined and passed for insurance. At that time a careful chest examination was made because of the above history of bronchopneumonia; this was found to be negative. Habits were normal and menstruation had not started. Home conditions were good, and there were no known tuberculosis contacts.

Onset of the present illness was about March 12; 1938 with cough, temperature of 101°F. and a slight weight loss. She was seen by her family physician, and chest examination at that time revealed râles over both lungs. In a few days this was followed by clinical findings of fluid in the left side. X-ray films (figures 1 and 2) made on March 16, 1938 were reported as follows: On the left side, there was a dense shadow occupying the entire upper lobe area, and a calcified area was seen in this shadow. The lower edge of the shadow was clear cut. There was also some clouding at the left base, which obscured the costophrenic angle. In the space between these two areas of great density, there was considerable peribronchial infiltration. On the right side, there was marked hilum infiltration with a few calcified nodes and marked fibrosis throughout the lungs. Both lungs showed definite X-ray evidence of an old inflammatory lesion. The consolidation at the left upper and at the left

[1] From the Pine Breeze Sanatorium, North Chattanooga, Tennessee.

[2] Presented at Staff Meeting, Pine Breeze Sanatorium, January 12, 1939.

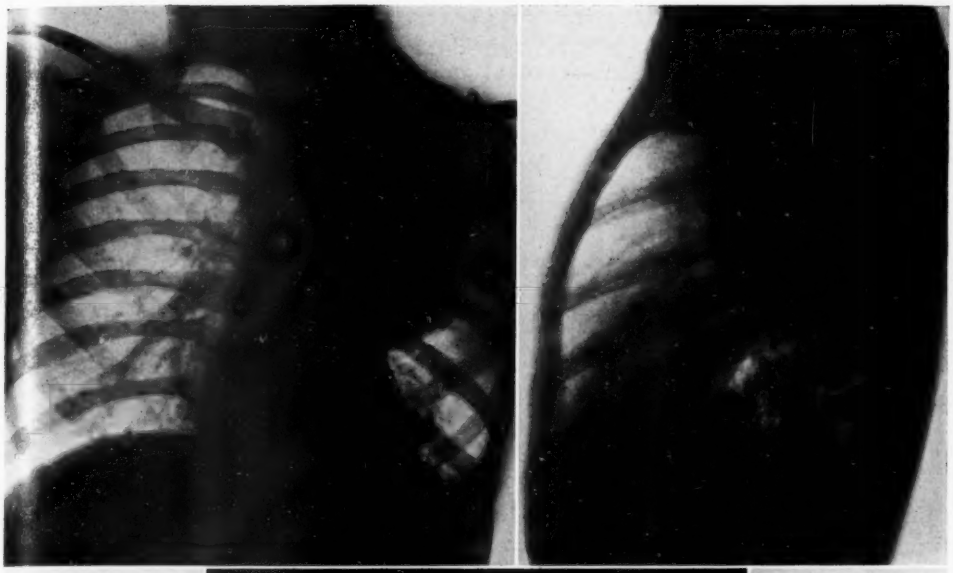

FIG. 1

FIG. 2

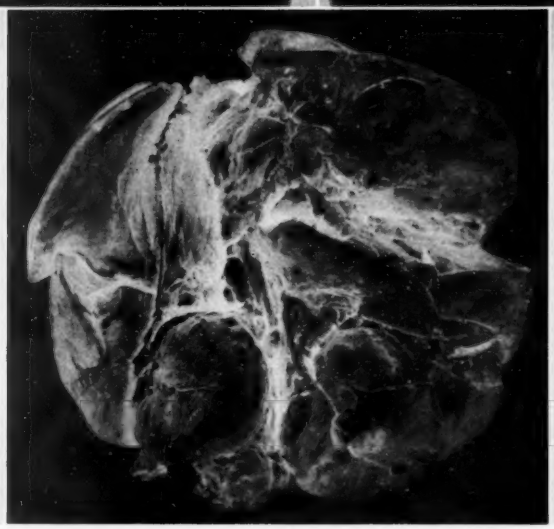

FIG. 3

FIG. 1. Stereoscopic view of chest made March 16, 1938
FIG. 2. Oblique plate of chest made March 16, 1938
FIG. 3. Anterior view of chest contents showing tumor in left upper lung. Autopsy specimen.

base most likely represents an inflammatory lesion, but the possibility of malignancy cannot be ruled out. The question of tuberculosis will have to be determined after a consideration of the clinical as well as the X-ray findings.

The patient was kept in bed and put on supportive measures. The temperature subsided, she gained 14 pounds, and appeared to be doing nicely. However, evidence of consolidation associated with diminished breath sounds remained in the left upper chest. This improvement lasted for only a short time. The cough became worse, and weakness and anorexia appeared.

A second X-ray film was made June 4, 1938. The findings follow: There is a dense shadow occupying the entire left half of the chest. From the present films it is impossible to tell how much of this shadow represents consolidation and how much is caused by fluid in the pleural cavity. Judging from the previous films, the lower half of the area probably represents fluid in the pleural cavity. The right lung area shows marked hilum and marked peribronchial infiltration, which shows no essential change since the time of the previous radiograph. Lesion, involving the entire left lung area, probably tuberculous infiltration at the upper lobe area and pleural effusion at the base.

Her condition grew progressively worse in spite of the supporting measures and it was impossible to control her cough. Weight loss was rapid and marked. Two weeks prior to admission to the hospital, following a spell of vomiting and coughing, she spit up about a half a cupful of foul smelling, purulent material.

Physical examination on admission revealed a white female, 12 years of age, of fair nourishment, slight build, and sallow complexion. The skin was warm and moist. Aside from generalized muscular weakness, all the abnormal physical findings were confined to the chest. On inspection there was a protrusion of the left anterior chest, and a slight depression in the left supraclavicular region. Expansion was shallow, and there was a lag on the left side. Percussion revealed flatness over the entire left chest. Breath sounds were absent over most of the left lung anteriorly and over the left upper chest posteriorly; they were diminished over the left lower chest. The right side of the chest was essentially negative.

Sputum was mucoid to mucopurulent. Many pus cells and many secondary organisms were seen in the last specimen examined. No acid-fast bacilli were found. The urine contained some albumen. A few casts and an occasional pus cell were seen. The haemoglobin varied between 61 per cent and 56 per cent, Sahli, the red cells between 3,250,000 and 3,070,000, and the white count between 33,400 and 41,750. The differential counts showed 9 to 16 per cent small lymphocytes and 78 to 86 per cent polymorphonuclear leucocytes of which 14 to 21 per cent were staff-forms, 64 to 65 per cent segmented, 0 to 2 per cent eosinophiles and 0 to 2 per cent basophiles; there were 1 to 5 per cent monocytes and 0 to 1 per cent Türck cells. Polychromatophylia, marked anisocytosis and some macrocytosis were present. One myelocyte was seen. On the day prior to death, bleeding time was five and a half minutes, coagulation time over sixteen minutes, and the platelet count was 131,930. The sedimentation rate was 27 mm. in sixty minutes.

Mantoux test and tuberculin patch test were negative.

X-ray examination of the chest on August 8, 1938 showed little change from the film of June 4, 1938, except that a slight shift to the right of the mediastinum was present.

Shortly after admission a thoracocentesis was done. A small amount of bloody fluid was obtained, but no laboratory examination was done on this. The patient was put on a selective diet and viosterol, and she was given sedatives. She maintained a progressively downward course with dyspnoea, severe cough, vomiting and loss of weight. On August 27 purpuric spots appeared over both thighs. The bulging of the left chest increased with notable rapidity, and there was progressive displacement of the heart to the right. The patient died September 1, 1938. Admission temperature was 102°F. and her daily temperature ranged from 98° to 102°F., usually being 100°F.

Autopsy was performed on September 1, 1938, about three hours after death, by Dr. F. B. Bogart. The body was that of a twelve year old white female, fairly well developed, but markedly emaciated. The left side of the chest was somewhat larger than the right side and appeared to bulge in the upper half. Ecchymosis was extensive and confluent over the anterior, inner and outer surfaces of both thighs.

Upon incising the skin the adipose deposit was found to be fairly well developed. On opening the thoracic cage, a small amount of straw colored fluid escaped from the left pleural cavity. The heart was markedly displaced to the right, lying almost entirely in the right side of the chest. The left upper ribs showed evidence of internal pressure.

Two large, firm masses were noticed at once. One of these, almost the size of a small grapefruit, occupied the upper anterior mediastinum while the other was situated in the left upper lung and apparently replaced most of the upper lobe. There were many adhesions around the left apex, but these were easily broken. The lungs, heart and mediastinal contents were removed *in toto* (figure 3), and examined at the end of the autopsy. Other findings were negative, except for fetal lobulation of both kidneys.

On examination of the left lung, a mass the size of a grapefruit occupied the upper lobe. This mass at first appeared to be separated from the smaller mass in the mediastinum by lung tissue. Upon closer examination the two masses were found to be one large mass measuring 12 x 14.5 x 9.5 cm. Lung tissue of the upper lobe had been consolidated and compressed outward and downward. The mass was clearly demarcated and the surrounding tissue could be peeled off from it.

Incision of the tumor revealed a cut surface that varied from dirty yellow to white in color. An area of calcification was present in the upper outer portion. The centre of the mass contained a large amount of caseous material. The tissue of the tumor appeared to be malignant rather than inflammatory in nature.

To the right and behind the mass there was a large abscess cavity filled with thick yellow pus. Another abscess was found inferior to the mass, and it involved both the upper portion of the lower lobe and the lower portion of the upper lobe of the left lung.

The left lower lobe showed some consolidation with honeycomb cavitation.

The right lung and heart appeared normal. There was no evidence of metastasis found.

Microscopic examination: The microscopical section from the tumor showed a loose connective tissue stroma infiltrated with a mixture of spindle cells and small round cells. There were areas in which the spindle cells predominated and other areas in which the small round cells were most prominent. There were no areas that showed definite giant cells. Numerous areas showed many capillaries and blood spaces.

Diagnosis: Mixed cell sarcoma, probably arising in the left upper lobe of the lung.

I wish to express my thanks to Doctors F. B. Bogart, W. E. Bryan and Doyle Currey for their assistance in reporting this case.

HAEMOPNEUMOTHORAX OF TUBERCULOUS AETIOLOGY

OREN A. BEATTY[1]

Jones and Gilbert (1) in summarizing 24 cases of haemopneumothorax found a relationship to tuberculosis in only 4 cases and noted that it differed from spontaneous pneumothorax only in the presence of haemorrhage. Birch (2) quoted Korol who considered the symptom complex in these cases characteristic and consisting of three stages, namely, (*1*) sudden pain and dyspnoea of spontaneous pneumothorax, (*2*) temporary improvement lasting hours or days and (*3*) recurrence of pain and signs of internal haemorrhage with physical signs of fluid and air in the pleural cavity. In a review of the literature cases are reported in which fluid is found upon first examination and, on the other hand, many are reported in which a pneumothorax alone is present in the beginning. Many case reports do not make this point clear but it is reasonable to believe that the spontaneous collapse precedes the haemorrhage.

The case reported herewith is a spontaneous pneumothorax with haemorrhage into the pleural cavity later. This case has particular interest because of the tuberculosis that has developed and been treated since and also because of a history of tuberculosis in the mother who was treated by pneumothorax and who died suddenly during the course of treatments.

Case Report

On August 27, 1937 a single, colored male, twenty years of age, walked into my office at 3:00 p.m., with body flexed forward at hips, holding hand over left chest, dyspnoeic, and complaining of pain. He stated the onset was at 10:00 a.m. when pain struck him suddenly while sitting in a chair at the drug store where he works as a delivery boy. He thought he had indigestion due to two pork chops which he had eaten for breakfast. He took soda and a carbonated drink which aggravated the pain.

It was evident that he was acutely ill and the severe dyspnoea directed the examination to the chest which gave physical signs of pneumothorax on the left side. This was corroborated by fluoroscopic examination which showed complete collapse of the left lung with the heart pushed into right side. No fluid was present. Fourteen hundred cc. of air were withdrawn following which fluoroscopic examination showed the heart in normal position and the left lung 75 per cent collapsed. There was an appearance of infiltration in the opposite lung above the clavicle.

[1] Chest Clinic, T. J. Samson Community Hospital, Glasgow, Kentucky.

He was sent home to bed and three hours later he had increased dyspnoea. It was observed that actually he was not as dyspnoeic as before but that he had more evidence of shock. Five hundred cc. of air were removed. Following this the patient was admitted to the hospital where thoracotomy with air escape through water valve was planned, but bright blood was encountered at the level of the eighth rib posteriorly. Operation was abandoned and 500 cc. of air were aspirated again through the sixth interspace posteriorly. The patient was given supportive treatment since it was considered that the symptoms following the first removal of the air were due to shock from haemorrhage rather than to the pneumothorax.

August 31, 1937, 500 cc. of dark blood were aspirated and 750 cc. and 350 cc. were aspirated on the 2nd and 6th of September, respectively. The patient was greatly improved and was discharged September 7.

Study of the patient while in the hospital gave the following facts regarding the history, physical and laboratory findings pertinent to his present illness.

His mother had moderately advanced pulmonary tuberculosis which was treated with pneumothorax on the left from June 11 to August 5, 1935, with a good collapse. August 8, 1935, while sitting in a chair, she fell forward and died suddenly at the age of forty-three years. No cardiac disease had been previously noted. One sister of the patient died in 1932 of tuberculosis at the age of twenty. Otherwise the family history was unimportant.

The general physical examination was essentially negative except that the patient was a young colored male, 73 inches high, weighing 160 pounds and markedly asthenic. The chest findings have been related before. The heart was apparently negative.

The pertinent laboratory findings were as follows: There was a slight trace of albumen in the urine on two occasions. The blood picture before aspiration of the haemothorax was: haemoglobin 80 per cent, red blood cells 4,500,000, and white blood cells 8,750 with 36 per cent lymphocytes and 64 per cent polynuclears. Upon discharge the blood picture showed 80 per cent haemoglobin, 4,200,000 red cells and 9,500 white cells with 26 per cent lymphocytes and 74 per cent polynuclears. The tuberculin test was four plus. An X-ray examination on August 30 showed a left pneumothorax with a fluid level at the fourth interspace. There was a small amount of infiltration in the right apex above the first rib. A follow-up X-ray film on September 15 showed complete reëxpansion of the left lung with no parenchymal infiltration. The infiltration in the right apex remained the same.

During the last week of January, 1938 the patient contracted a deep cold with a cough, began to expectorate mucous and mucopurulent material, had night sweats and ran fever. At the time of reporting to the clinic, March 24, he had a severe cough with profuse expectoration, fever of 100.6°F., a pulse rate of 120, and loss of weight from 168 to 143 pounds. There were physical

signs of disease in the right lung and X-ray examination showed marked infiltration, fibrosis and an inflammatory process to the fourth rib and seventh vertebral spine. There was multilocular cavity formation throughout the upper third. The left lung was clear. The sputum was positive for tubercle bacilli.

Artificial pneumothorax treatments were advised for the right lung and the initial treatment was given April 12. These have been continued and at the present time he is taking approximately 500 cc. at three-week intervals with a good collapse. The patient has improved and gained weight. The last X-ray film on June 7 showed the left lung, which was the site of the spontaneous pneumothorax, clear with no narrowing of the intercostal spaces and no thickened pleura. A definite fibrous band has appeared in the left apex. The right lung showed an area of pneumothorax with approximately 75 per cent collapse. Several string-like adhesions were in the upper portion but apparently not interfering with the collapse. There was a broad adhesion to the diaphragm and a small amount of fluid in the angle.

DISCUSSION

This patient's symptoms more or less conform to the symptom complex of Korol. The stage of temporary improvement in this case followed the removal of air by pneumothorax. Following this there were signs of internal haemorrhage. The tension of the spontaneous pneumothorax may have caused a tear into the lung tissue, and the removal of the air may have relaxed the pull on torn vessels and initiated the haemorrhage.

In a review of the literature the author was struck by the frequent description of the patient as the asthenic type in both spontaneous pneumothorax and haemopneumothorax. In those cases in which no reference was made to the type the X-ray appearance was that of the asthenic individual. It was not remembered that any reference was made to a spontaneous pneumothorax occurring in the opposite type. The patient reported herewith was markedly asthenic, as was also his mother. At the time of the sudden death of his mother the author was at a loss to account for the death since no autopsy was obtained. No heart disease was recognized at the time and it was very unlikely that she had a cerebral accident. Since the occurrence of the haemopneumothorax in her son in the good lung, it seems probable that a spontaneous pneumothorax may have occurred in the mother in her better and uncollapsed lung. Priest (3) reported a case of sudden death from bilateral spontaneous pneumothorax in a young man who had no tuberculosis on postmortem examination.

CONCLUSIONS

A case of nontraumatic spontaneous haemopneumothorax of probable tuberculous aetiology in a young asthenic colored male is reported.

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CULTURE METHOD IN SPUTUM EXAMINATION[1]

Its Value in Patients from Tuberculosis Field Clinics

JOHN LOESCH AND FRANK PETRIK

It is rather easy to establish a definite diagnosis of tuberculosis on patients admitted to a hospital where repeated sputum examinations can be made and where the clinical and X-ray findings can be most critically evaluated. The converse, however, is true in Out-Patient Departments or in Itinerant Field Clinics where patients are seen only once or at relatively long intervals. In these instances, a great deal of time is necessarily lost before the diagnosis of tuberculosis is established and the patient placed under proper treatment.

Unfortunately, in these clinics, although the patients are examined physically and by X-ray, the sputum is examined infrequently, if at all. In those instances where positive sputum is obtained by examining smears, it is rarely more than a confirmatory finding. We know from our experience that cultural studies bring to light many cases during the evolution and regression of the disease, when frequently small tuberculous foci in the small bronchi persist for a long time in the absence of physical signs and of definite X-ray findings. As the amount of sputum and the bacillary content is minimal in these cases, it is necessary to collect the sputum in a sterile glass container for at least three successive days to ensure the highest number of positive results.

In order to be an aid in detecting early or hidden pulmonary tuberculosis, the sputum examination has to be as exhaustive as possible. It is the common practice to examine sputum by direct smear and, if it is negative, then by the concentration method. To prove whether or not these two methods are sufficiently delicate to detect the greatest number of positive cases by laboratory examination, we have, for the past year and a half, cultured all sputa which were negative on concentration. The medium and procedure of the culture method employed in this investigation has been described in detail by one of us (1).

Guinea pig inoculation, which is held as the most sensitive test for the demonstration of tubercle bacilli, was not done, because in our experience and in that of many investigators, such as Norton, Thomas and Broom (2), Murphy and Duerschner (3) using the Petragnani medium, and Hirschberger (4) selecting Corper's, Hahn's and Miraglia's medium,

[1] From the Laboratory of the Homer Folks Tuberculosis Hospital, Oneonta, New York.

the culture method is equal to animal inoculation if sufficient material is seeded. Positive results depend in general on the extent of surface inoculation. It was found by us that the inoculation of at least four to six tubes, 6 x ¾ inch, is needed to equal the results obtained by guinea pig inoculation. Further, it would be very difficult, even impossible, for many laboratories to inoculate routinely two pigs per case to safeguard against the loss from intercurrent disease. The great number of animals that would be required for this type of examination precludes this method from becoming the accepted practice in most laboratories.

To make the sputum examination, the patient was given by the examining physician a suitable container and requested to collect and mail about one-half an ounce of sputum, or, if the expectoration was slight in amount, all of the sputum raised for three successive days. The purulent, flaky sputum was first examined by direct smear. If negative, it was examined by the concentration method as were those other specimens which were mucoid, or liquefied and watery. If the concentration examination was also negative, material from the same sediment was seeded on four tubes of culture medium. In 31 instances there was insufficient material to culture after the concentration was negative and for various reasons further examination could not be made.

The positive results of the examinations of sputa in 1,028 cases by direct smear, concentration and culture were as follows:

Positive direct smear	79
Positive concentration	37
Positive culture	36

Review of the obtained results shows that, of 1,028 cases, 860 were negative on smear and concentration, but of this negative group 36 cases (4. 18 per cent) were positive on culture. These culturally positive cases would have been missed had only the direct smear and concentration methods been used. In other words, it shows very clearly that these methods are insufficient to detect the maximal possible number of positive cases, especially when a minimal number of bacilli is raised. The culture method is a simpler means of examination than guinea pig inoculation; it gives in most instances definite findings in positive cases within two or three weeks, and it is less time-consuming, laborious and more economical, which is a matter of considerable importance if many examinations are being made.

In addition, acid-fast colonies, different from the human tubercle bacillus, and variants of the latter in association with colonies of the human strain on the same tube were frequently demonstrated that would have been missed on animal inoculation. We have encountered them in 24 cases during the last two years and they offer a fruitful material for an interesting study on acid-fast organisms. The results of this investigation will be reported later.

Critical evaluation of these findings raises an important question: Is it worth while to examine smears from the concentrated material obtained from clinic patients? In this series, 949 smears of concentrated material had to be examined to detect 37 positive cases. A tremendous amount of time is consumed in preparing, staining and examining these slides—and economy of time must be considered in a busy laboratory. Might it not, therefore, be more economical to culture all sputa immediately after they are found negative on direct smear?

SUMMARY

A total of 1,028 sputum examinations on the same number of clinic patients are reviewed.

When the culture method was used to supplement smear and concentration, 24 per cent of the total number of positive cases were detected by culture only.

The economic advantages of this method are self-evident.

It is suggested that all sputa which are negative on direct smear be cultured.

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TUBERCULIN PATCH TEST[1]

A Comparison with the Mantoux Intracutaneous Test

GRANT TAYLOR

The Morro, Pirquet, Mantoux and various plaster-ointment tests (1, 2, 3, 4) have been, at one time or another, advocated to replace Koch's original subcutaneous tuberculin test. The modifications have attempted to achieve a reliable test which could be applied quickly and painlessly and which would evoke no untoward reaction. Such a test should be readily acceptable, particularly in this country, where there is such an intensive campaign being waged in our public schools against tuberculosis.

The tuberculin patch test devised by Dr. Hermann Vollmer appears to have met these requirements, for in a series of 118 children admitted in the pediatric service of Mount Sinai Hospital, New York City, and a series of 209 tuberculous children on which the Pirquet and the patch test were done simultaneously, very satisfactory results were obtained. Results equally as gratifying were experienced in a series of 169 tuberculous children tested simultaneously with the tuberculin patch test and the Mantoux test using PPD (5, 6, 7).

In the autumn of 1937 a series was started at Duke Hospital, Durham, North Carolina. All subjects were given simultaneously (in a few instances two months elapsed between the Mantoux and the patch test) 0.1 cc. of 1:1,000 dilution of OT intracutaneously and the patch test. Both arms were prepared in the usual manner by washing thoroughly with acetone-alcohol and drying. The OT and control solution were injected into the right arm and the patch test was applied to the left arm. The subjects were advised that they might take baths but to maintain the patch in position until their return for observation in forty-eight hours. At this time the Mantoux test and control were read and the patch removed. Sensitiveness to adhesive tape sometimes obscures the accurate reading of the patch test, and in many instances there is a delayed tuberculin reaction, so all subjects were advised to return again in twenty-four hours for the final reading of their patch test. The subjects included whites and Negroes and were chosen at random from the following groups: nurses, medical, law and engineering students, hospital staff, and ward patients, both children and adults. The ages ranged from three months to seventy-one years. The results of these tests are presented in table 1.

[1] From the Department of Bacteriology and the Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

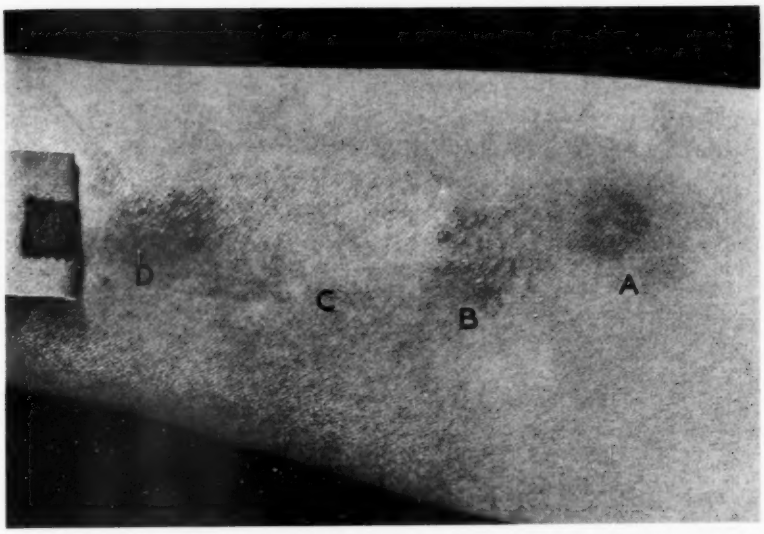

FIG. 1. Comparison of reaction of injection of 0.05 cc. of 1:1000 OT and patch test at 48 hours.

A = positive Mantoux reaction; B and D = positive patch test (papular-vesicular rash with surrounding erythematous area); C = negative control area of patch test.

TABLE 1

	+ PATCH + MANTOUX	− PATCH − MANTOUX	+ PATCH − MANTOUX	− PATCH + MANTOUX
Nurses	64	161	14	1
Students	40	106	12	2
Children				
White	10	35		
Colored	4	15		
Ward patients				
White	18	89	1	7
Colored	30	52		3
Miscellaneous				
White	12	33		1
Colored	13	20		1
	191	511	27*	15†‡
	25.7%	68.6%	3.6%	2.01%

* Twelve of these 27 were retested with 0.1 cc. of 1:100 OT and were found to be positive with this dilution.

† Of these 15 subjects, 12 ranged from fifty-two to seventy-one years of age, and 3 from twenty-two to twenty-four years of age, thus possibly indicating that the texture of the skin in older people might be responsible for the negative patch test.

‡ Total 744 cases.

COMMENT AND OBSERVATIONS

The Vollmer patch test seems to be slightly more sensitive than the Mantoux test in young adults, and less sensitive in persons above the age of fifty years. In no case was there a reaction more serious than a severely itching skin rash. In subjects giving such a reaction, the Mantoux test frequently resulted in a markedly painful reaction of the arm leading to a sloughing of the tissues.

A few subjects, especially small children, react to the adhesive tape; however, this nonspecific rash in such cases disappears in a few hours after the removal of the tape and in no way interferes with the reading of the test.

At least seventy-two hours should elapse after the patch is applied before the result is declared negative. The test is as easily read in the colored as in the white race. In mild reactions either end of the patch may give a positive reaction; in more severe reactions both ends usually react. Only one increase in temperature attributable to the tests was recorded in 744 cases. On small children the patch was found to remain in place better if applied to the sternum or across the trapezius muscle.

CONCLUSIONS

1. A total of 25.7 per cent of subjects gave a positive Mantoux and a positive patch test; 68.6 per cent gave a negative Mantoux and a negative patch test. Thus, the two tests yielded comparable results in 94.3 per cent of 744 persons tested.

2. In 3.6 per cent a negative Mantoux and a positive patch test were observed; of these 27 subjects, 26 were found among young adults, students and nurses.

3. In 2.0 per cent a negative patch test and a positive Mantoux were seen; of these 15 subjects, 12, or 80 per cent, were above fifty years of age.

In this series of 744 cases in which the Vollmer patch test was compared with the Mantoux intracutaneous test, using 0.1 mg. OT., the results indicate that the simpler Vollmer test is equally as effective as the Mantoux test, and possesses many advantages for the physician as well as for the patient.

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STATISTICAL DATA

Edited by JESSAMINE S. WHITNEY

MORTALITY RATE, 1938

With this issue of the Review, a new statistical service is inaugurated. The editors plan to present current statistical data and the results of various research studies in the field of tuberculosis as they become available. This service will appear about six times a year.

This month a table is presented showing the number of reported cases and deaths from tuberculosis, by states, for the year 1938. These data have been obtained by direct correspondence with the health officers of the various states. The resulting death rate for the entire United States, namely, *48.6*, is 9.3 per cent below that of 1937, and indicates the greatest single annual decline in the past three decades, except for the phenomenal fall in the rate during the few years just after the peak of 1918.

The decline in the tuberculosis death rate over the thirty-year period is shown in the accompanying graph. It is to be noted especially that the rate of decline since the World War and the devastating influenza pandemic of 1917–1918 has been accelerated.

CASE-FINDING

A new but very interesting and fertile field for case-finding in tuberculosis has been found in general hospitals which have no special provisions for tuberculosis cases. A study recently made in New York State, where fourteen general hospitals made a routine chest X-ray of all cases admitted, revealed 47 persons with significant lesions, or 1.2 per cent of the nearly 4,000 patients who have been X-rayed to date. In a report[1] commenting on these data, the author says:

Of the active cases discovered, 19 had evidence in their hospital charts indicating that the attending physician may have diagnosed the case before discharge. However, 28, or 0.7 per cent of adult admissions, were found to have active tuberculosis and there was no evidence in the hospital records which indicated at the time of admission that tuberculosis was suspected. If the same con-

[1] *Evaluation of Various Techniques of Case-Finding* by Robert E. Plunkett, M.D. Read at the Thirty-fourth Annual Meeting of the National Tuberculosis Association, 1938.

New cases reported, deaths, and death rates from tuberculosis, by states, 1938

(Provisional figures as reported by state departments of health)

STATE	NEW CASES REPORTED*	NUMBER OF DEATHS	CASES PER DEATH	DEATH RATE PER 100,000
United States	108,076	63,332**	1.71**	48.6**
Alabama	2,784	1,604	1.74	55.0
Arizona	1,298	862	1.51	206.7
Arkansas	909	1,003	0.91	48.8
California	7,670	4,033	1.90	65.1
Colorado	711	655	1.09	60.6
Connecticut	1,201	613	1.96	34.9
Delaware	144	131	1.10	50.4
District of Columbia	1,468	588	2.50	92.2
Florida	1,177	987	1.19	58.8
Georgia	3,011	1,612	1.87	51.8
Idaho	209	106	1.97	21.4
Illinois	8,222	3,686	2.23	46.5
Indiana	2,007	1,380	1.45	39.4
Iowa	776	488	1.59	19.0
Kansas	629	428	1.47	22.8
Kentucky	1,588	1,972	0.81	67.0
Louisiana	2,116	1,432	1.48	66.6
Maine	521	253	2.06	29.5
Maryland	3,002***	1,333	2.25	78.7
Massachusetts	3,594	1,684	2.13	37.8
Michigan	6,335	1,866	3.39	38.3
Minnesota	1,929	815	2.37	30.5
Mississippi	1,324	1,102	1.20	53.9
Missouri	2,564	1,828	1.40	45.4
Montana	499	239	2.09	43.7
Nebraska	203	220	0.92	15.9
Nevada	99	71	1.39	68.3
New Hampshire	212	142†	1.49	27.8†
New Jersey	4,148	1,962	2.11	44.8
New Mexico	808	392	2.06	91.2
New York	15,680	6,539	2.40	50.1
North Carolina	2,607	1,876	1.39	53.4
North Dakota	244	136	1.79	19.0
Ohio	5,742	3,090	1.86	45.5

* A special effort was made to obtain the number of new cases reported exclusive of those which have been designated as the "childhood type" of tuberculosis which in some states are reportable. The figures here presented are as furnished in accordance with this instruction except where otherwise indicated.

** Total mortality adjusted to include deaths from all forms of tuberculosis in Virginia. Ratio of cases to deaths based on total mortality which includes only the pulmonary deaths in Virginia.

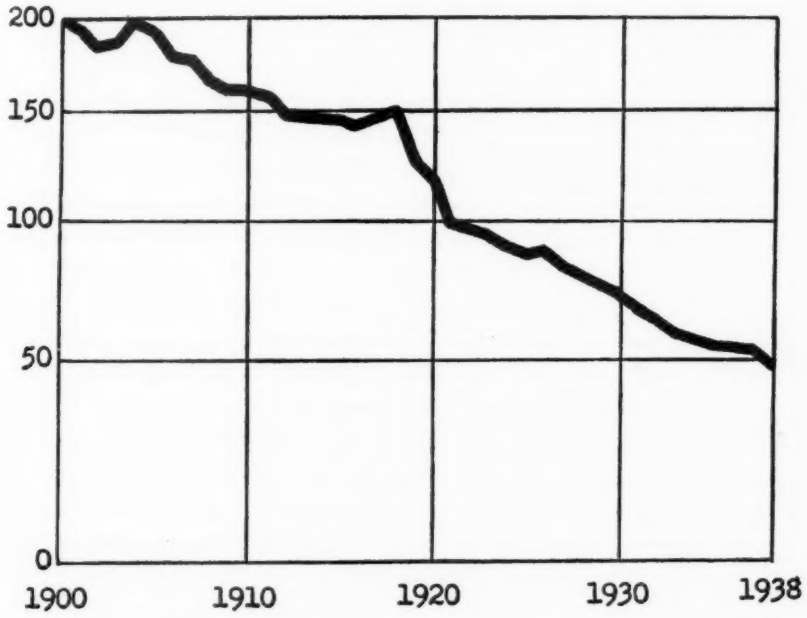
*** Includes "childhood type" cases.

† 1937 deaths and rate as reported by state health department; 1938 figures not available.

New cases reported, deaths, and death rates from tuberculosis, by states, 1938—Concluded

STATE	NEW CASES REPORTED*	NUMBER OF DEATHS	CASES PER DEATH	DEATH RATE PER 100,000
Oklahoma	1,300	1,162	1.12	45.3
Oregon	676	305	2.22	29.6
Pennsylvania	4,559	4,348	1.05	42.4
Rhode Island	494	277	1.78	40.1
South Carolina	866	917	0.94	48.6
South Dakota	244	230	1.06	32.7
Tennessee	3,375	2,180	1.55	74.7
Texas	3,600	4,119	0.87	66.3
Utah	214	99	2.16	19.0
Vermont	130	147	0.88	37.6
Virginia	2,207‡	1,636‡	1.35‡	60.1‡
Washington	1,462***	718	2.04	43.1
West Virginia	1,751	932	1.88	49.7
Wisconsin	1,760	912	1.93	31.0
Wyoming	7	56	0.13	23.9

‡ Pulmonary only. (All forms—deaths—1,802 in 1938)



TUBERCULOSIS DEATH RATES SHOWING RATE OF DECLINE
United States Registration Area, 1900 - 1938
Vertical Scale is Logarithmic

dition prevailed throughout the United States, about 45,000 unrecognized cases of tuberculosis were admitted to general hospitals during 1937.

FRAMINGHAM DEMONSTRATION

The impetus given to health work by the intensive Health Demonstration in Framingham, Massachusetts in the years 1917 to 1923 is reflected in present day figures there. The Demonstration was made possible by a grant from the Metropolitan Life Insurance Company and was conducted by a committee of the National Tuberculosis Association. The latest reported tuberculosis death rate from Framingham is 17 per 100,000 for the year 1938. At the time the Demonstration began, namely, 1917, the tuberculosis rate for the state of Massachusetts was 145.9 and that for Framingham, 97.5. For 1938, the Massachusetts tuberculosis rate was 37.8 as compared with the very low rate of 17 for Framingham.

EXTRAPLEURAL PNEUMONOLYSIS WITH PARAFFIN FILLING[1]

Late Results

R. B. McINDOE,[2] JOHN D. STEELE, JR.[3] AND JOHN ALEXANDER[4]

Extrapleural pneumonolysis with paraffin filling in the treatment of pulmonary tuberculosis was first proposed by Baer (1) in 1913. This procedure has been used fairly extensively in Europe since that time, although its use in this country is still limited. Since European surgeons were obtaining satisfactory results with the operation, and since patients were frequently being seen for whom all other collapse therapy procedures were contraindicated, although the need for some surgical measure was apparent, the operation was adopted by the Division of Thoracic Surgery of the University of Michigan in October, 1930. Since that time it has been used 124 times for 105 patients.

We feel that an extrapleural paraffin pneumonolysis is definitely indicated in certain groups of patients having apical lesions not extending below the second rib anteriorly and with cavities 4 cm. or less in diameter which cannot be closed by the induction of pneumothorax or by phrenic nerve interruption. The first group is a relatively small one in which the risk of thoracoplasty is not great, but in which the risk of an extrapleural paraffin pneumonolysis is even smaller and in which it seems almost certain that the latter operation will suffice for closure of the cavity. The second group is larger, and consists of patients who are poor thoracoplasty risks because of inadequate respiratory functional reserve, advanced age or because their general condition is poor. In the third group, thoracoplasty is definitely contraindicated because of too active tuberculosis in the contralateral lung, certain types of extrapulmonary tuberculosis or other disease.

In the management of patients with bilateral pulmonary tuberculosis,

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the availability of a considerable variety of collapse therapy procedures is distinctly advantageous. The addition of paraffin pneumonolysis to the list of available procedures has resulted in the arrest of the disease in many patients with bilateral lesions who would otherwise have been denied the benefits of collapse therapy. Bilateral paraffin pneumonolysis can be performed with relative safety. Furthermore, we have used paraffin pneumonolysis successfully in a number of patients having a small apical cavity in the contralateral lung after the use of a thoracoplasty on the side with the more extensive involvement. The performance of a bilateral thoracoplasty, on the other hand, is a hazardous and, frequently, an unsatisfactory procedure.

During the first four years of our experience with extrapleural paraffin pneumonolysis, this operation was performed much more frequently than it has been in the last four years. The reason for this decrease in the number of operations is not that we have become less enthusiastic about its use, but that the technique of thoracoplasty has been so greatly improved that it has been possible to perform carefully staged thoracoplasties on patients who five years ago would have been considered unsuitable risks for this procedure.

An anterior approach was used for the extrapleural paraffin pneumonolyses performed during the first two years of our experience with this operation. It was soon discovered, however, that the posterior approach was preferable for the following reasons: first, satisfactory extrapleural cleavage could be obtained much more frequently with the posterior approach and, consequently, the results as to cavity closure were better; and second, because of the thickness of the muscles posteriorly, closure could be made more solidly with less danger of extrusion of the paraffin (2). For these reasons, the use of an anterior approach was abandoned six years ago except as a supplementary operation. Since we no longer recommend the use of the anterior approach, the results in the group of patients in which it was used will be only briefly summarized.

The first anterior operation was performed on October 18, 1930, and the last on January 18, 1933. Of the 23 patients who had primary anterior paraffin pneumonolyses, only 10 are living to-day. Six of these are apparently cured; 2 are apparently arrested; and 2 still have active pulmonary tuberculosis. Three of the 6 patients who are apparently cured subsequently had thoracoplasties performed over the paraffin fillings. The causes of death in the other 13 patients were as follows: 8 died from progression of pulmonary tuberculosis; 3 died as a direct result of the

operation; one died following the second stage of a thoracoplasty which was being performed over the paraffin; and one died of heart disease six years after an effective paraffin pneumonolysis.

These results are poor, first, because satisfactory extrapleural cleavage was obtained in only 50 per cent of the cases, and second, because attempts were made in this early experimental period to close cavities larger than those now considered suitable for closure by paraffin pneumonolysis.

Our first primary posterior extrapleural pneumonolysis with paraffin filling was performed on December 23, 1931. The last patient included in the group now being reported was operated upon on October 21, 1937. The operation was performed 90 times upon 82 patients, of whom 74 patients had unilateral and 8 had bilateral fillings. There were 6 supplementary anterior fillings, making a total of 96 operations.

The technique of the posterior operation has been described in detail by Alexander (3). The operation can usually be performed with local anaesthesia. A short parascapular incision is made and a 6 cm. portion of the third or fourth rib is resected. The periosteal bed is incised and extrapleural cleavage is performed with the finger in the plane of the endothoracic fascia. Optimal collapse is dependent upon the absence of firm extrapleural adhesions. Undue force must not be exerted in the separation of such adhesions because of the danger of tearing the lung. After the apex of the lung has been freed on all sides and has retracted, the extrapleural space is ready for the paraffin filling. Sterilized paraffin, having a melting point of 52°C., is heated and allowed to cool until it is easily malleable, without crumbling, and is then gently laid in the extrapleural space without pressure in masses of from 15 to 25 g. each, fitting the masses together so as to eliminate dead space. The last mass is flattened into the shape of a button so as to act as a barrier to the extrusion of the other masses. The use of more than 300 g. of paraffin is avoided, first, because of the danger of pressure on the mediastinal structures, and second, because of the danger of reducing the vital capacity below the limits of safety in certain patients. (In our present series of cases, the size of the fillings averaged 248 g.) Each muscle layer is closed separately with great care, using catgut sutures. The paraffin soon becomes enveloped by a firm capsule of fibrous tissue, which, in a few months, will reach a thickness of from 2 to 3 mm.

In order to ascertain the present status of the 82 patients who had primary posterior paraffin pneumonolyses, questionnaires were sent to all known living patients. The status of these patients was determined

by roentgenological examinations and sputum examinations made within six months of the completion of this study (July 1, 1938) with the following exceptions: 7 patients had satisfactory roentgenological and sputum examinations within a year; 8 patients had no recent roentgenological examinations (usually for financial reasons) but, of the 8, 7 are working full time, 4 have had recent sputum examinations and 3 have no expectoration.

The present status of 76 of our 82 patients is known (table 1). Seven patients failed to reply to the questionnaires and could not be located; 6 of these are classified as untraced; the seventh was discharged from the sanatorium as apparently arrested only eight months before the completion of this study and so was not listed in table 1 as untraced.

In all except a few instances, the roentgenograms were reviewed by one or more of the authors. An effort was made to obtain adequate sputum examinations. Negative direct smears were followed by concentrates and cultures when possible. The results of sputum examinations in the 69 traced living patients were as follows: 24 patients had smears only, 7 smears being positive and 17 negative; 10 had concentrates but no cultures, the 10 concentrates being negative; 21 had cultures, one being positive and 20 being negative; 9 patients had no expectoration, and 5 patients who had sputum failed to submit specimens for examination.

Fifty-four (78.4 per cent) of our 69 traced living patients are apparently cured, arrested or apparently arrested. It will be noted in table 1 that the quiescent group includes 5 patients recently operated upon who are still in sanatoria and, although their cavities are closed and the sputum is negative, their exercise has not been increased sufficiently to permit them to be included in the apparently arrested group.

The operative risks presented by our patients have been classified into three groups with respect to the possibility of thoracoplasty. The risk was estimated on the basis of the general condition of the patient, the age, the presence or absence of active disease in the contralateral lung, etc. Of the 82 patients, 21 (25.4 per cent) were good thoracoplasty risks, 26 (31.8 per cent) were poor thoracoplasty risks, and in 35 (42.8 per cent) thoracoplasty was definitely contraindicated. In classifying these patients into these groups we have used our present day standards as to fitness for thoracoplasty. These standards have changed considerably in the past three or four years and we now perform carefully staged thoracoplasties without much hesitation on patients who would formerly

have been considered poor or unsuitable risks for this procedure. Some of our patients who had been regarded as poor risks for thoracoplasty when their paraffin pneumonolyses were performed four or more years ago have been reclassified as good risks, and some in whom thoracoplasty was previously considered contraindicated have now been included in the poor risk group. Thus the above figures do not accurately represent the relative percentages of these groups according to our present indications for extrapleural paraffin pneumonolysis.

TABLE 1

*Present status of 82 patients with paraffin pneumonolysis**

	PATIENTS	PER CENT	AVERAGE MONTHS SINCE OPERATION†
Apparently cured	31	37.8	60
Arrested	14	17.1	30
Apparently arrested	9	11.0	30
Quiescent**	9	11.0	30
Improved	4	4.8	30
Unimproved	2	2.4	24
Dead	7	8.6	
Untraced	6	7.3	
Total	82	100.0	

* Classifications in this table conform to the Diagnostic Standards of the National Tuberculosis Association (1935 edition).

** The quiescent group includes 5 patients recently operated upon whose cavities are closed and whose sputum is negative.

† By mere chance these accurate figures happen to be in multiples of six.

Fifty-four (78.4 per cent) of the 69 traced living patients are apparently cured, arrested or apparently arrested.

The results as to cavity closure are given in table 2. In compiling this table, we have included the results of the following: 61 traced living patients having unilateral operations; 3 patients having unilateral operations who have since died from causes unrelated to their paraffin pneumonolyses; 8 traced living patients having bilateral operations, counting each patient as two cases (the bilateral cases will be considered separately later). Thus table 2 gives the results of 80 operative procedures performed upon 72 patients. Not included in this table are the following: 6 untraced patients; 3 patients whose deaths are attributable to the operation; one patient who subsequently died from progression of his pulmonary tuberculosis. Considered as cases (counting the patients

having bilateral operations as two cases) cavity closure was obtained in 68, or 85 per cent; considered as patients, cavity closure was obtained in 60, or 83.4 per cent.

It will be noted in table 2 that the results in the patients in whom thoracoplasty was contraindicated were the least satisfactory because the paraffin pneumonolysis was used as a last resort operation in some patients with relatively little hope of closing cavities larger than 4 cm. in diameter. Of the 43 cases in the first two groups (on whom thoracoplasty might have been performed) cavity closure was obtained in 41, or 95.3 per cent. This high percentage of cavity closure should not be directly compared with the percentage of cavity closure in series of thoracoplasty cases, since the latter usually includes a considerable proportion of patients with large cavities.

TABLE 2

Results as to cavity closure in 72 traced patients surviving the operation with each of eight patients having bilateral operations counted as two cases, or a total of 80 cases

CLASSIFICATION OF PATIENTS WITH REGARD TO POSSIBILITY OF THORACOPLASTY	CAVITIES CLOSED		CAVITIES NOT CLOSED	
	Cases	Per cent	Cases	Per cent
Good thoracoplasty risks	18	90	2	10
Poor thoracoplasty risks	23	100	0	0
Thoracoplasty contraindicated	27	73	10	27
Totals	68	85	12	15

One of the disadvantages of an extrapleural paraffin pneumonolysis is that it is sometimes impossible to determine by means of an ordinary posterior-anterior roentgenogram whether or not the cavity has been closed by the operation. The reason for this is that the paraffin is partially radiopaque and an open cavity lying anterior or posterior to the filling may be obscured. We routinely make use of lateral views and the Potter-Bucky diaphragm in following these patients after operation. In the final analysis, the sputum examination may have to be relied upon to determine whether or not the cavity has been closed, provided, of course, that there is no active lesion in the contralateral lung.

Although not used in connection with our present series, we recognize the possibility that some form of sectional roentgenography (such as tomography or laminography) may be the most satisfactory method of determining whether or not cavity closure has been effected by the operation.

As might be expected, our results were best in those cases in which satisfactory cleavage was obtained and in which the apex could be freed extrapleurally and brought down to the desired level. Such satisfactory dissection was possible in 55 (69 per cent) of our cases and was followed by cavity closure in 51 (92.9 per cent). Cleavage was unsatisfactory because of dense extrapleural adhesions which could not be safely divided in 25 (31 per cent) with the result that the cavities were closed in only 17 (68 per cent). In a few patients no cleavage plane could be found and the operation had to be abandoned; these patients are not included in any of our statistics, as no paraffin was introduced.

The operation was most successful in closing relatively small cavities. The fate of all cavities according to size is given in table 3. Of the 43 cavities 2 cm. or less in diameter, 40 (93 per cent) were closed by the operation. An attempt was made as a last resort in 6 patients to close cavities larger than 4 cm. in diameter, closure being effected in 4 (66.6 per cent).

TABLE 3

Fate of all cavities according to size

SIZE (DIAMETER IN CM.)	NUMBER	CLOSED	NOT CLOSED	PER CENT CLOSED
0–0.5	4	4	0	100.0
0.6–2.0	39	36	3	92.3
2.1–4.0	38	31	7	82.0
4.1–6.0	6	4	2	66.6

The fate of cavities in regard to their type was analyzed. Using Pinner's classification, we found the results with respect to cavity closure to be as follows: moth-eaten cavities, 93 per cent were closed; round or oval cavities, 70 per cent were closed; cavities with heavy irregular walls, 89 per cent were closed.

Eight patients had bilateral paraffin pneumonolysis. The operation was successful in closing the cavities on both sides in 4 patients and the cavities on one side only in the other 4. Subsequent clinical improvement in 2 of the latter patients permitted the ineffectual unilateral paraffin fillings to be removed and thoracoplasties to be performed. The thoracoplasty in one of these patients has been completed successfully. In the other patient, it was not completed because of the discovery of a myelogenous leukaemia. The condition of the remaining 2 patients, whose disease is controlled on one side only, will not, as yet, permit

removal of the paraffin on the active side and the performance of a subsequent thoracoplasty.

Subsequent operations were performed upon 11 patients because of failure of the posterior extrapleural paraffin pneumonolysis to close their cavities. Six patients had supplementary anterior paraffin pneumonolyses; 4 patients had thoracoplasties following the removal of the paraffin fillings; one patient had a thoracoplasty over the paraffin.

The cavities of 4 of the 6 patients who had supplementary anterior paraffin penumonolyses were closed by the anterior stage.

Thoracoplasty was contraindicated as the primary operation in the 4 patients who eventually had this operation following the removal of the paraffin fillings. Even though their cavities were not closed by the paraffin fillings, subsequent clinical improvement permitted thoracoplasties to be performed later. There is no contraindication to removing the paraffin and performing a thoracoplasty when necessary, provided, of course, that the condition of the patient permits. Head (4) has recommended the use of paraffin pneumonolysis in preparation for thoracoplasty in large apical cavities and has reported good results from the combination of these two procedures. We have not, however, used this combination deliberately.

In the case of the only patient who had a thoracoplasty over the paraffin, the cavity had almost closed following the paraffin pneumonolysis, but later increased markedly in size. The thoracoplasty was successful and the patient is now apparently cured.

The number of postoperative complications was relatively small (table 4). Twelve patients had transient dyspnoea requiring the administration of oxygen. The three wound infections were all superficial to the muscle layer. Postoperative haemorrhage into the extrapleural space occurred in 2 patients. In one case it was necessary to remove the paraffin in order to control the bleeding; in the other, aspiration of the blood about the paraffin was necessary because of dyspnoea. The formation of serous fluid about the paraffin required aspiration for the relief of dyspnoea in 2 other patients. The one patient who expectorated the small piece of paraffin a few days after operation had no further complications.

We have not listed fever under "immediate postoperative complications" because it occurs in almost all cases. The fever usually rises to between 101° and 103°F. on the first postoperative day and persists for about one week. Only 2 patients failed to develop fever of at least

100°F. The fever is probably due to an autotuberculinization, although the introduction of the foreign body may be a factor in some cases and, of course, the large surgical wound inevitably causes some fever.

Simple tuberculous infection of the extrapleural space resulting in cold abscess formation about the paraffin occurred in 3 patients. In one patient it was necessary to remove the paraffin two months after operation. This patient subsequently died from a mixed infection of the extrapleural space and progression of her pulmonary tuberculosis. The cold abscess of another patient was discovered when the paraffin was removed three years after operation, because of expectoration of paraffin and a persistently positive sputum. The cold abscess of the third patient was extremely small and was discovered accidentally at

TABLE 4

Postoperative complications (96 operations)

A. Immediate Complications	
Transient dyspnoea	12
Superficial wound infection	3
Haemorrhage into extrapleural space	2
Fluid formation about paraffin, requiring aspiration	2
Tuberculous spread to contralateral lung	1
Expectoration of small piece of paraffin	1
Pyogenic infection of extrapleural space	0
B. Late Complications	
Cold abscess formation about paraffin	3
Expectoration of small pieces of paraffin	4
Extrusion of paraffin through wound	0
Sinking or migration of paraffin	0

autopsy ten months after the paraffin pneumonolysis, following death from a cause unrelated to the pulmonary tuberculosis.

Four patients expectorated slivers of paraffin within several years following the operation. One is untraced. The removal of the paraffin of another has already been mentioned. The 2 other patients are known to be still expectorating paraffin. One of these was operated upon five years ago. His cavity is closed, his sputum is negative, and he is working full time, although he occasionally expectorates a small sliver of paraffin. The other patient's cavity is unclosed and her sputum is positive. Her general condition will not permit further surgical therapy at the present time. In general, we do not feel that the mere expectoration of paraffin is necessarily an indication for its removal.

Of the 7 deaths listed in table 1, 2 are directly attributable to the operation (an operative mortality of 2.4 per cent). One patient had a severe immediate postoperative reaction and died of bronchopneumonia five days after removal of the paraffin for suspected infection of the extrapleural space. The other patient died two months after operation with severe dyspnoea and signs of mediastinal embarrassment.

The death of the third patient (eight months after operation) following cold abscess formation about the praffin has already been mentioned.

The fourth patient died from progression of his pulmonary tuberculosis several years after the operation.

There were 2 late deaths from causes other than tuberculosis. The pulmonary lesions of these patients were inactive at the time of death, the cavities being closed and the sputum negative in both instances. One patient died, four years after his paraffin pneumonolysis, from pernicious anaemia; the other died, ten months after pneumonolysis, following the administration of a spinal anaesthetic preparatory to an operation for a ruptured appendix.

The seventh patient died following an open intrapleural pneumonolysis of the contralateral lung five years after a successful paraffin pneumonolysis had been performed.

EXTRAPLEURAL PARAFFIN PNEUMONOLYSIS VERSUS EXTRAPLEURAL PNEUMOTHORAX

Before concluding, we will consider the advantages and disadvantages of extrapleural paraffin pneumonolysis as compared with those of extrapleural pneumothorax. The indications for these two procedures may appear to be similar in certain cases. We did not discuss extrapleural pneumothorax in connection with the indications for paraffin pneumonolysis at the beginning of this article because only one of our paraffin pneumonolyses was performed after we had started to consider the use of extrapleural pneumothorax; therefore there was virtually no conflict of indications between the two operations in the cases presented. We are now occasionally faced with a choice between the two procedures. A consideration of the relative merits of the two operations includes the following:

First, extrapleural paraffin pneumonolysis is rarely successful in closing cavities larger than 4 cm. in diameter since it is dangerous to use more than 300 g. of paraffin in attempting such closure. Extrapleural pneumothorax may, however, be successful in closing much larger cavities.

Second, extrapleural pneumothorax is a revocable operation, at least within a short time after its induction, and, if intolerable dyspnoea should occur, refills may be abandoned. In this respect it has an advantage over paraffin pneumonolysis which is not revocable after a stiff fibrous tissue capsule forms around the paraffin.

Third, the collapse obtained after a paraffin pneumonolysis is never lost, while an extrapleural pneumothorax space may sometimes be difficult or impossible to maintain.

Fourth, in a patient with a low respiratory reserve, in whom more than a very limited apical collapse is contraindicated, a paraffin pneumonolysis has a distinct advantage over an extrapleural pneumothorax. While small apical lesions can often be controlled with the use of from 100 to 300 cc. of paraffin, an extrapleural space of the same capacity would be too small to be maintained successfully by extrapleural pneumothorax, and a much more extensive collapse would be necessary if the latter procedure were used.

Fifth, some authors have reported discouraging results when extrapleural pneumothorax has been used in an attempt to close old cavities with thick walls. Our results with paraffin pneumonolysis in this type of cavity have been far from discouraging.

Sixth, we feel that the incidence and the severity of the complications of extrapleural pneumothorax are as great, if not greater, than those which we have encountered in the use of paraffin pneumonolysis. We believe, for instance, that the danger of early and late infection of the extrapleural space is decidedly greater in extrapleural pneumothorax.

Seventh, since extrapleural pneumothorax is a relatively new operation, the end results are not known. We have, on the other hand, followed some of our paraffin patients for more than six years and know better what to expect from this procedure. In a case in which all other considerations were of equal weight, we would choose the paraffin pneumonolysis for this reason alone. We are, however, using extrapleural pneumothorax in cases which do not seem to be suited for either thoracoplasty or for paraffin pneumonolysis.

COMMENT

We are convinced that extrapleural paraffin pneumonolysis is an effective operation and that it is indispensable in certain patients in whom all other surgical collapse procedures are contraindicated. We also feel that a considerable operative mortality has been avoided in a group of poor risk patients who would otherwise have been subjected to

thoracoplasty. The success of extrapleural paraffin pneumonolysis is dependent upon strict adherence to the indications as outlined and to a meticulous observance of the details of an approved operative technique. We recommend the operation only in patients having apical cavities 4 cm. or less in diameter which cannot be closed by the induction of pneumothorax or by phrenic nerve interruption. Extrapleural paraffin pneumonolysis can be used successfully in some patients who are not suitable thoracoplasty risks. Whether or not extrapleural paraffin pneumonolysis should be used as a substitute for thoracoplasty in patients who are suitable for thoracoplasty depends upon the circumstances in individual cases. Our results in this group of patients have been extremely satisfactory. The safety of the operation, in any case, is essentially dependent upon a cautious extrapleural dissection, upon the avoidance of the use of too large a filling and upon gentleness in the handling of the patient's tissues.

SUMMARY

1. The results of the use of posterior extrapleural pneumonolysis with paraffin filling in a group of 82 patients have been reviewed.

2. Of the traced living patients, 78.4 per cent are classified as apparently cured, arrested or apparently arrested.

3. Cavity closure was obtained in 83.4 per cent of the patients surviving the operation.

4. The operative mortality was 2.4 per cent.

5. Early and late complications were relatively infrequent.

6. The indications for extrapleural pneumonolysis with paraffin filling are compared with those for extrapleural pneumothorax.

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COLLAPSE THERAPY OF TUBERCULOSIS[1,2]

Seen from the Viewpoint of Control of the Disease in the Community

ALLAN J. HRUBY

I would like to preface my remarks on collapse as an instrument of community welfare by a brief review of the control measures exercised in Chicago prior to the collapse era. In Chicago, for many years, control of open tuberculosis has shaped the axis of the tuberculosis drive. Since 1917, isolation of the contagious case from children under sixteen years of age has been mandatory. The child and the consumptive parent or guardian may not live in the same house; one or the other has to go. The mechanisms involved in breaking the contact, preventorium for the child, institutional care of the open case, familial adjustments, placarding and forcible hospitalization for the recalcitrants, are too intricate to receive detailed consideration here. Suffice to say that over the years from an average of 3,500 known, open cases resident in the City, only about 35 or 40 at any one time were in contact with children, these 35 or 40 representing the residue of difficult cases in process of clearance.

On the face of it these results might have seemed satisfactory. In reality, both from the humanitarian and the civic viewpoint, such was very far from being the case. Backed by the State regulations, we would compel the patient to leave his home and family; unfortunately, however, we could not tell him where to go. Accommodation was lacking. In 1931, when the present Board of Directors took office, there were 700 patients on the Sanitarium waiting list, the majority of whom were contagious cases. Similar waiting lists prevailed at Cook County Hospital and Oak Forest, the two other free institutions. The picture was disturbing. Looking at it in one way it seemed all right; looking at it against another light it showed certain unpleasant shadows and distortions. How much good had really been achieved? How far was community betterment advanced by the measures of isolation in vogue? True, individual children in individual homes were benefited and safe-

[1] From the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Read at the annual meeting of the New York Tuberculosis and Health Association, New York City, March 2, 1939.

guarded. In how far was this benefit neutralized by the increased community menace, personalized by the infectious patient existing apart from his family, living as best he might in lodging houses or rooming houses, eating in cheap restaurants, and very probably endangering other children in street cars, movie houses and similar places? To sum it all up, the lot of the dispossessed case was far from enviable, the benefit to the community problematic.

In an attempt to meet the problem in a more humanitarian way, the Board of Directors added 121 beds to the Sanitarium proper and opened another 300-bed institution, originally called the Municipal Home for the Open Case. Labor lost! The waiting lists remained the same. As the head of the queue disappeared into the Sanitarium to take possession of the new beds, the tail lengthened with discouraging persistency. We still had 700 patients on the waiting list. Obviously we had neither solved the health problem of the patient nor met the social indication. The patients grew from bad to worse, and the community continued to be endangered by the hundreds, even thousands, of cases for whom no institutional accommodation was available; 20,000 registered cases in Chicago and only a total of 2,471 beds (1,500 in the Municipal Tuberculosis Sanitarium, 337 in Cook County Hospital and 634 in Oak Forest). That was the problem.

To meet the double need, the health problem of the patient and the social problem of the community, we came at last to the only recourse available, collapse of every suitable case in the Sanitarium, pneumothorax in the field from the initial injection onward. Concerning the field program we had our doubts. In 1931 collapse outside the institution was frowned upon. In many quarters we encountered head-shaking and dire prophecy, and felt our purpose waver as we listened to the litany of the dangers and pitfalls that confronted us—air embolism, spontaneous pneumothorax, haemorrhage, accidents in the home or on the street cars to or from the clinic, difficulty of follow-up, etc.

Despite all this, and after some hesitation, the directors of the Sanitarium decided to pursue their course. The situation was urgent, the well being of the individual patient and the welfare of the community constituted a double objective, and large scale collapse seemed to meet them both. We could not take the patient to the Sanitarium; we could, perhaps to some extent, take the Sanitarium to the patient. The effects of collapse on the lesion were well known, the effects of collapse on the sputum were well known. Was it possible to put these two well estab-

lished facts to practical application against our problem? In the absence of an alternative, why not? To the directors of the Municipal Tuberculosis Sanitarium, harassed by waiting lists, imbued with the necessity of doing something, collapse in mass application seemed, at one and the same time, a measure of hope for the individual otherwise doomed and a public health instrument of great potentialities.

Before going further it is, perhaps, necessary to say a word concerning the organization and administrative set-up which made the experiment less hazardous than it seemed. Tuberculosis in Chicago is the sole responsibility of the Municipal Tuberculosis Sanitarium. The institution, operating under the Glackin Act, is managed by a board of three directors who have entire charge of both the field and the Sanitarium. As a consequence, a close coördination between intramural and extramural activities is possible. In the new collapse plan this coördination was to be exploited to the limit. The patient in his presanatorium, sanatorium and postsanatorium life was to be subjected to a uniform and sustained policy. Collapse at the Sanitarium was to be stepped up to keep pace with the collapse in the field, and each branch was to supplement and enhance the activities of the other.

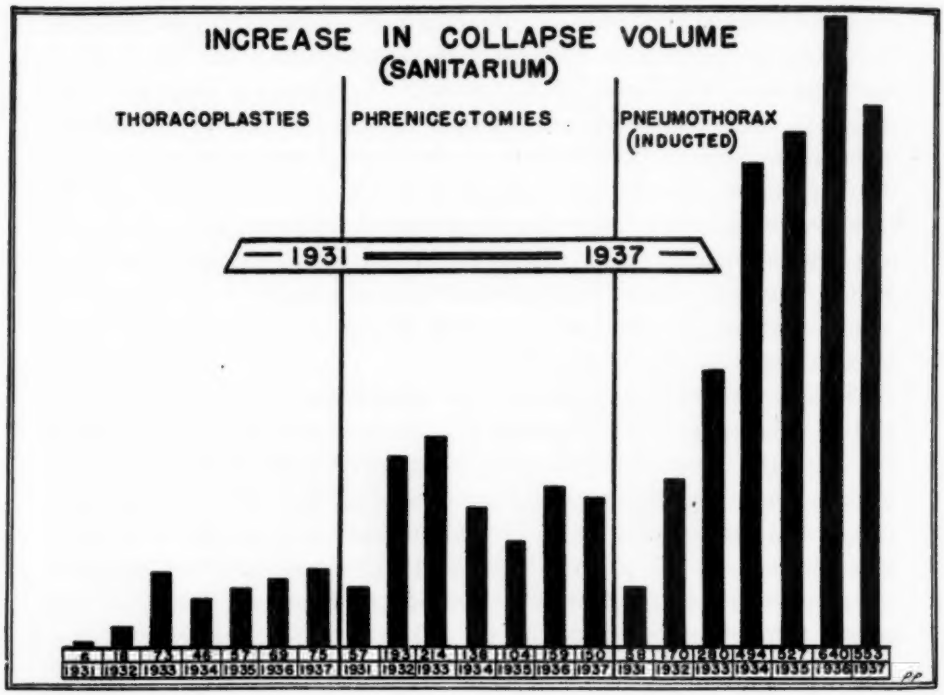
The advantages of a program thus unified are obvious; reciprocity, mutual enlargement, the discharge of refill cases from the Sanitarium to the field, the admission of complicated cases from the field to the Sanitarium. As a corollary, greater good to a greater number, increased tempo and faster turnover in the Sanitarium; in the field a sense of security built on the premise that institutional facilities were available when necessary. The debatable question of follow-up was to be answered through prompt visits by the 151 field nurses; that of complications in the home was to be met by the portable X-ray and pneumothorax at the bedside.

A word as to technique. At the inception of the program every one of the 1,200 odd patients at the Sanitarium was examined for collapse possibilities. Those considered suitable were referred for final decision to the Selection Committee, composed of the Medical Superintendent, the attending chest surgeon and selected members of the staff. In the field, all diagnosed cases were referred to a similarly organized committee and all new X-ray plates taken throughout the entire dispensary system were ordered sent to the same body.

In April, 1931, after exhaustive instruction with special reference to positive sputum as the public health indication, the new program was

started. At that time, 121 cases were under collapse, of one kind or another, at the Sanitarium proper. Seventy-two discharged cases whose pneumothorax had been instituted at the Sanitarium were receiving refills at one of the dispensaries.

The present report represents a study of 8,083 charts and constitutes an attempt to evaluate the results of large scale collapse over the period January 1, 1931 to July 1, 1936. Of the 8,083 charts studied, 742 were

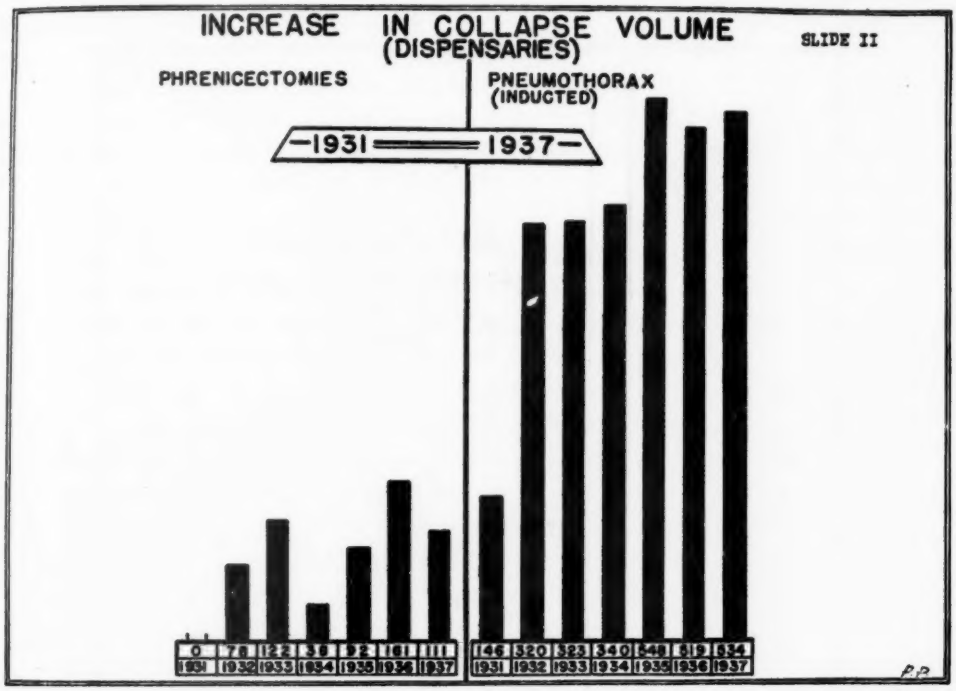


GRAPH 1

thrown out as unsuitable for the following reasons: disputed diagnoses, nontuberculous diseases, records incomplete, pneumothorax or other procedure on nontuberculous conditions, such as bronchiectasis, abscess, etc., cases registered before July 1, 1936, the dead line for acceptance but not subjected to collapse until shortly after this date, cases begun or finished elsewhere for whom complete data were unavailable. There were left, then, discarding these 742 patients, 7,341 charts which sifted out as follows:

Cases treated over three months	3,090
Cases treated less than three months	337
Pneumothorax attempted	330
No pneumothorax attempted (refusal, adhesions, noncoöperation, failure to return, disciplinary discharge, and various other reasons)	3,584

The growth of the program since 1931 is seen in graph 1. As will be noted, pneumothorax inductions at the Sanitarium rose from 58 in 1931,



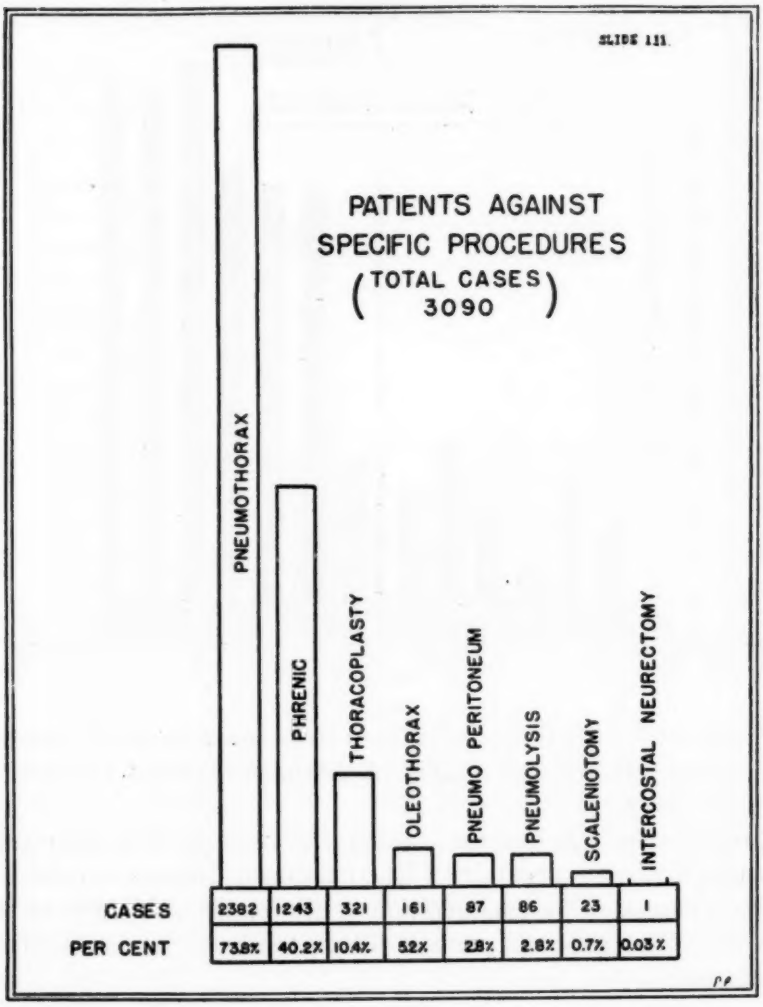
GRAPH 2

to 553 in 1937. By the end of 1931, 6 thoracoplasties and 57 phrenicectomies had been done, as against 75 thoracoplasties and 150 phrenicectomies in 1937.

Graph 2 shows the increase in collapse work in the dispensary system. The graph is self-explanatory. The increase in collapse volume is still better exemplified by consideration of the numbers actually receiving treatment throughout the period. The figures are shown in the following tabulation:

Patients Receiving Collapse Treatment during Period 1931–1938
(Dispensaries)

1931	173
1932	455
1933	697
1934	893
1935	1,139
1936	1,591
1937	1,523
1938	2,036



GRAPH 3

Graph 3, including both the Sanitarium and the dispensary cases, shows the relative incidence of the various procedures. The study covers all patients treated between January 1, 1931 and July 1, 1936. Pneumothorax, it will be seen, is almost twice as frequent as its nearest competitor, the phrenic operation. Thoracoplasty, with 10.4 per cent, seems to us rather high. Ideally, thoracoplasty should be a comparatively rare operation. I used to say that the thoracoplasty of to-day is the result of the ignorance of yesterday. That is, perhaps, too sweeping. While it is possibly true that tuberculosis sufficiently advanced to demand thoracoplasty predicates ignorance somewhere along the line—patient, physician, community—it is none the less true, in view of the many factors operative against early diagnosis, that thoracoplasty has come to stay. It is our aim, nevertheless, to lengthen the pneumothorax and phrenic columns and decrease thoracoplasty, an aim avowedly difficult in view of the fact that 80 per cent of the cases when first seen in the dispensaries of the Municipal Tuberculosis Sanitarium are advanced.

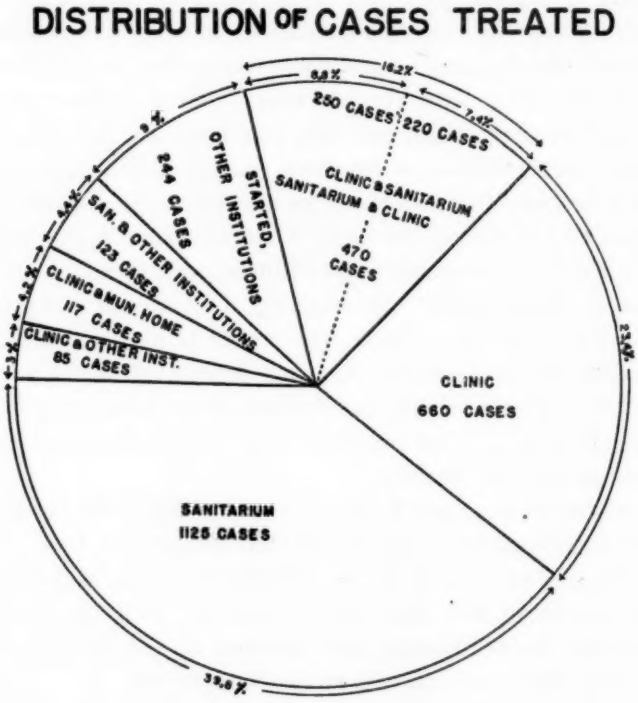
Next, as to distribution. In studying a combined program of intramural and extramural collapse, the reader is naturally interested in the percentage of cases treated by each branch of the service. How many cases were treated in the Sanitarium alone, how many in the field clinic alone, how many had combined field and Sanitarium treatment? Graph 4 shows the distribution.

As demonstrated in graph 4, 39.8 per cent of the 2,824 collapsed cases were treated exclusively in the Sanitarium proper, 23.4 per cent of the cases were treated exclusively in the extramural clinic, and 16.2 per cent were treated both in the clinic and Sanitarium. Of the total, 7.4 per cent started at the Sanitarium and finished at the clinic, 8.8 per cent started at the clinic and finished at the Sanitarium.

The technique of the survey included recent X-ray and reëxamination of all cases under treatment; the same, or the equivalent, for all dismissed cases brought within reach by the following measures: nurse's visit to the home to bring in patient for examination, nurse's investigation of the neighborhood to locate lost cases, similar investigations in other dispensary districts for patients that had moved, gas company and post office inquiries, letters, first-class mail to last known address, letters and questionnaires to private physicians, to patients out of town and to other institutions. Of the treated cases, 89.3 per cent of the Sanitarium patients were traced and fully studied, as against 93.7 per cent of the clinic cases, and 92.5 per cent of those who received treatment at both the

clinic and Sanitarium. In view of the volume and the circumstances, the socio-economic bracket involving the average type of patient, and the percentage of migratory workers in a large American city, these figures, a total of 8.6 per cent lost in 3,090 cases, may be considered satisfactory.

Whether the results themselves are satisfactory or otherwise may well be a matter of opinion. The estimation of collapse results is notoriously



GRAPH 4

difficult. We may as well say here and now, and without further preface, that *the control* at best is a doubtful equation. In a disease as protean and unpredictable as pulmonary tuberculosis it is impossible now, and always will be, to set off against each other any two groups of cases with identical or even similar diagnostic facets and prognostic features. No two cases are alike. Even were they alike to-day, we have no assurance that some weeks or months hence the same two cases will not be as far apart as cavity and cicatrix.

In view of all this we cannot afford to be too arbitrary. On the one hand we must attempt to avoid overenthusiasm; on the other hand we must not allow ourselves to be discouraged as we turn the pages of a journal to read unfavorable figures on collapse. We must accept with some reservation, statistical studies drawn from the questionnaire and compilations from the literature. In a similar vein, we must view with some caution tabulations based on presumptive morbidity against official mortality. The latter procedure, recently practiced both here and abroad in an attempt to analyze the social significance of collapse, is apt to be deceptive. Morbidity is an unknown quantity, the case report a creature of its environment. The true incidence of tuberculosis is one thing, the reported incidence another, and both phases of the question are subject to modifying influences that destroy the value of morbidity as a base.

Equally misleading are the analyses based on sanatorium mortality ratios in the precollapse era as compared with the ratios current at this time. Sanatorium mortality is not a constant. There are too many variables, intangibles, imponderables, changing policies of admission with changing administrations, more actual than relative sanatorium accommodation now than formerly, with greater latitude in the admission of advanced cases. One also has to bear in mind the recent trend of advanced tuberculosis toward the sanatorium for collapse. In view of these and other factors, how can we take a group of sanatoria, or even one sanatorium, and establish mortality ratios as a base? It is impossible. The admissions regulate the deaths; the number that die will depend on the composition of the material at the gate, and the material at the gate is a question of policy.

The matter of a suitable control for collapse is, then, admittedly difficult. For lack of better we accepted the usual measuring rods, *pneumothorax attempted, pneumothorax under three months* and *no collapse.* The material was bad. In our study of 3,090 treated cases, 94.2 per cent of the patients had advanced tuberculosis, 84.4 per cent of the cases had positive sputum, and 81.3 per cent cavity for the cases studied from this viewpoint. Add to this 439 Negroes (14.2 per cent) who must be considered against their background, the existent tuberculosis mortality in Chicago, a ratio of six to one in favor of the white. With this picture before us and bearing in mind the reservations mentioned, what were the actual results? Table 1 gives the first split. As will be seen, of the 3,090 treated cases, 69.3 per cent were known to be living at the date of

the report, as against 33.0 per cent of the controls, figures that indicate a survival ratio of better than two to one in favor of the treated cases.

The results according to the classification of the National Tuberculosis Association are arranged in a study of the 6,403 traced cases in table 2. Looking at the tabulation and comparing the figures from the angle of the National Classification, arrested, quiescent and improved, the ratio of two to one in favor of collapse is again well sustained.

TABLE 1

Present status—7,341 total cases

		LIVING		DEAD		UNTRACED	
		Number	Per cent	Number	Per cent	Number	Per cent
Treated over three months	3,090*	2,142	69.3	682	22.1	266	8.6
Under three months	337	113	33.5	175	51.9	49	14.6
Pneumothorax attempted	330	130	39.4	146	44.3	54	16.3
No collapse	3,584	1,184	33.0	1,831	51.1	569	15.9
Total all cases	7,341	3,569	48.6	2,834	38.6	938	12.8

* Including permanent collapse procedures as well as pneumothorax.

TABLE 2

Results at final examination according to the National Classification—6,403 cases

	TOTAL CASES	ARRESTED		QUIESCENT		IMPROVED		UNIMPROVED		DEAD	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Over three months	2,824	893	31.7	392	13.9	586	20.7	271	9.6	682	24.1
Under three months	288	31	10.8	28	9.7	34	11.8	20	6.9	175	60.8
Pneumothorax attempted	276	33	11.9	24	8.7	39	14.1	34	12.4	146	52.9
No collapse	3,015	514	17.1	218	7.2	216	7.2	236	7.8	1,831	60.7
Totals	6,403	1,471	23.0	662	10.3	875	13.7	561	8.8	2,834	44.2

We come next to what we consider a major feature in the program, the public health aspects of collapse. As already mentioned, the campaign in Chicago has, for many years, been oriented toward the isolation of the carrier. The difficulties and defects of personal isolation have been discussed. What influence may be attributed to the new form of attack, mechanical isolation of collapse? Has this mechanical isolation advanced the cause of community control? Table 3 gives the results in

the 6,403 cases studied.[3] As will be seen, including all cases, 53.9 per cent of the treated cases were converted from positive to negative, as against 15.3 per cent in the controls. Since the inception of the program in 1931, 1,285 cases, all still living, all still sputum-clean, have been converted from positive to negative. In all, 1,285 "fountains of infection" have been shut off, a townful of carriers made safe for the community. When you realize that practically all these cases came from heavily congested districts where the possibilities of spreading infection are abundant and ripe, the gain to the community may be appreciated. The complete splits on this question of sputum conversion will be given in a coming Bulletin of the Municipal Tuberculosis Sanitarium, soon to be

TABLE 3

Conversions—6,403 total cases

		POSITIVE		CONVERSION		REMAINED POSITIVE		DEAD	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Treated over three months	2,824	2,384	84.4	1,285	53.9	417	17.5	682	28.6
Treated under three months	288	253	87.8	38	15.0	40	15.8	175	69.2
Pneumothorax attempted	276	244	88.4	59	24.2	39	16.0	146	59.8
No collapse attempted	3,015	2,441	81.0	374	15.3	236	9.7	1,831	75.0

released. For the present I will advert to only one phase, the degree of conversion crossed against the stage of disease.

Of the 66 positive minimals treated and still living, 56, or 84.8 per cent, have been converted and are still negative. Of the 565 moderately advanced positives, 454, or 80.4 per cent, have been converted and are still negative. Of the 1,071 far advanced cases treated and still living, 775, or 72.4 per cent, have been converted and are still negative. True

[3] The criteria on which the conversions were based follow the rules and regulations of the State Board of Health (Illinois) as laid down in the following paragraph: "All known cases of pulmonary tuberculosis or consumption, in which a positive sputum has been obtained, shall be considered as 'open cases' for at least a period of three months, and thereafter until three successive specimens of sputum, collected at intervals of one week, shall have been found to contain no tubercle bacilli upon examination at a laboratory approved by the Illinois Department of Public Health, the physical examination of the patient indicating that the type of tuberculosis present in the patient be such as would coincide with the findings of a negative sputum."

some of those cases, especially in the more recent groups, will undoubtedly relapse.

This brings up another question, the permanency of collapse results in general. Are the immediate effects illusory? What is the picture after some years have elapsed? Table 4 indicates the general results as classified, from 1931 to 1936 inclusive. It will be seen that 64.3 per cent of the cases treated previous to 1931 are living as against 31.3 per cent in the controls. The figures for the subsequent years, as the tabulation shows, run in similar ratio. Looking at sputum conversion from the same angle, of the 1,215 positive sputum cases converted, 894, or 73.5

TABLE 4

Year of initiation or date of registration or admission against end results—5,839 total cases

PREVIOUS TO		TOTAL CASES	LIVING		DEAD	
			Number	Per cent	Number	Per cent
1931	Treated over three months	171	110	64.3	61	35.7
	No collapse	421	132	31.3	289	68.7
1931	Treated over three months	154	103	66.9	51	33.1
	No collapse	329	121	36.7	208	63.3
1932	Treated over three months	427	284	66.5	143	33.5
	No collapse	387	162	41.8	225	58.2
1933	Treated over three months	511	359	70.2	152	29.8
	No collapse	487	185	37.9	302	62.1
1934	Treated over three months	521	398	76.4	123	23.6
	No collapse	477	162	33.9	315	66.1
1935	Treated over three months	630	523	83.0	107	17.0
	No collapse	610	269	44.1	341	55.9
1936	Treated over three months	410	365	89.0	45	11.0
	No collapse	304	153	49.6	151	50.4

per cent, at the time of the report had been consistently negative for a period of over one year. Of these, 227 had been negative from two to three years, 154 had been negative from three to four years, 94 from four to five years, 27 five to six years, and 25 six years and over. Consideration of these figures should dispel the myth that sputum change is an ephemeral phenomenon of no importance to the community.

In a paper of this length it is difficult to pick out, from the hundreds of tabulations made, the studies which may prove most suitable.

Table 5 showing type of treatment against results in the 3,090 treated cases may be of interest. Thoracoplasty and other collapse with 82.4 per cent living shows strangely enough the best results. Davison's

report on his 393 thoracoplasties is quoted in full in the Bulletin of the Municipal Tuberculosis Sanitarium, soon to be released.

Another tabulation which is certainly of interest in a paper dealing with community influence checks end results against race (table 6). Studying the figures, it will be seen that the ratio is in favor of the white,

TABLE 5

Type of treatment against results—3,090 treated cases

Cases treated over three months

	TOTAL	LIVING		DEAD		UNTRACED		PER CENT OF KNOWN CASES LIVING
		Number	Per cent	Number	Per cent	Number	Per cent	
Pneumothorax only	1,509	1,057	70.0	321	21.3	131	8.7	76.7
Phrenic only	475	295	62.1	152	32.0	28	5.9	65.9
Pneumothorax and phrenic	470	328	70.0	92	19.4	50	10.6	78.0
Pneumothorax and pneumonolysis	45	33	73.4	12	26.6	0	0	73.4
Pneumothorax and oil	110	80	72.8	21	19.1	9	8.1	79.2
Thoracoplasty only	70	47	67.2	15	21.4	8	11.4	75.8
Thoracoplasty and other collapse	254	183	72.1	39	15.3	32	12.6	82.4
All other treatment	157	119	75.8	30	19.1	8	5.1	79.8
Total	3,090	2,142	69.3	682	22.1	266	8.6	75.8

TABLE 6

End results against race—6,270 whites, 1,071 negroes—7,341 total

	TOTALS			PER CENT KNOWN CASES LIVING		
	White	Black	Total	White	Black	Total
Treated over three months	2,651	439	3,090	78.9	57.4	75.8
Treated under three months	260	77	337	44.6	21.2	39.2
Pneumothorax attempted	233	97	330	55.2	29.1	47.1
No collapse	3,126	458	3,584	39.0	38.8	39.2
Totals	6,270	1,071	7,341	57.7	44.4	55.7

78.9 per cent living as against 57.4 per cent. When we take into consideration, however, that in Chicago the death rate in the Negro is six times that of the white, the difference is not discouraging.

On the whole we are inclined to think that collapse is an influential instrument in the control of tuberculosis in the Negro. The question is of great civic importance in Chicago where, with a Negro population

of 250,000, 7 per cent of the total population accounts for 35 per cent of the deaths. Nor is Chicago alone concerned. Control of tuberculosis in the Negro is a national problem and permeates every community. It is surprising that the inherent possibilities of collapse for the members of this race have been studied so little. With a population of twelve million Negroes, about 225,000 who need hospitalization for tuberculosis and only about 7,500 beds to receive them, extramural collapse would seem to offer at least a large fraction of solution. In any plan dealing with control of the disease in large communities, it must be realized that the Negro carries an undue proportion of open tuberculosis. Consequently, and logically, he should receive his share of attention, a share graduated generously in proportion to the urgency of his problem.

TABLE 7

Sanitarium versus clinic—2,824 cases treated over three months

	TOTAL CASES	ARRESTED		APPARENTLY ARRESTED		QUIESCENT AND IMPROVED		UNIMPROVED		DEAD	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Clinic	777	144	18.5	89	11.5	212	27.2	72	9.3	260	33.5
Sanitarium	1,248	139	11.2	188	15.0	499	40.0	121	9.7	301	24.1
Combined	799	190	23.8	143	17.9	267	33.4	78	9.8	121	15.1
Total	2,824	473	16.7	420	14.9	978	34.7	271	9.6	682	24.1

Since this paper deals with the control of the disease in the community, and since extramural collapse is a necessary implement in community control, you will doubtless wish to know the relative results as between collapse done in the Sanitarium and in the field. Table 7 gives the data. Looking at the table and combining all better classifications, the clinic shows 57.2 per cent arrested, quiescent and improved, as against 66.2 per cent for the Sanitarium and 75.1 per cent for clinic and Sanitarium combined; 33.5 per cent dead for the clinic as against 24.1 per cent dead for the Sanitarium, and 15.1 per cent for the group receiving both clinic and Sanitarium treatment. The figures seem logical, good results for the field, better for the Sanitarium, best for the combination of Sanitarium and extramural collapse.

It may be alleged, and with some justice in view of ideas already enunciated, that the controls are not accurate, that the groups are not similar, that the study failed, as all large studies on collapse must, in establishing

anything approaching identity of symptoms, comparability of pathology and prognosis. All right! Let us try another measuring rod. Bear in mind, as we do, the type of tuberculosis dealt with in this report, 94.2 per cent advanced, 84.4 per cent positive sputum. How does disease of this kind turn out? What is the outlook for the bacilliferous patient? What is his life expectancy? Bad! Very bad!

In the type of patients seen by municipal institutions in metropolitan centres, positive sputum in from 75 to 90 per cent of the cases is a death warrant within five years. This is no mere idea. The fibre and irrevocability of the death warrant were demonstrated by a study of all open cases registered with the Municipal Tuberculosis Sanitarium prior to the year 1927. Of the 8,779 cases studied, 82.96 per cent were dead at the end of five years, 91.16 per cent were dead at the end of ten years. These

TABLE 8

Air embolism versus pneumothorax treatments—field clinic only

YEAR	TOTAL TREATMENTS	EMBOLIC ACCIDENTS	RATIO OF TREATMENTS TO AIR EMBOLISM
1931	1,376	3	459:1
1932	4,666	6	778:1
1933	7,457	7	1,065:1
1934	10,796	2	5,398:1
1935	16,627	4	4,157:1
1936	19,003	5	3,800:1
1937	23,320	1	23,320:1

figures have been amply corroborated by William Farr, Prindle, Kayser-Petersen, Lissant Cox, the London County Council Reports and other sources. Let us take, for example, the London County Council Reports. These Reports, involving a turnover of approximately 4,000 cases a year, show an average survival rate after five years of 32.0 per cent for the moderately advanced positive case and 5.0 per cent for the far advanced. Compare this with a survival rate of 69.3 per cent in our series.

There is still another control, a measuring rod which the scientist, perhaps, will not accept but which, nevertheless, has its values for the man in actual contact with collapse procedure. I refer to the implications, feelings and convictions of those doing the work, to the consensus among phthisiotherapists everywhere as to the value of collapse. The man who actually sees the improvement, who sees acute tuberculosis halted and chronic tuberculosis cured, can afford to be skeptical of results

based on the fallible essence of the questionnaire; his patients are his tabulations.

In a paper of this size it is impossible to deal, in any length, with the complications encountered. I will discuss merely one, air embolism, and further restrict discussion to the accidents encountered in the field. The tabulation (table 8) tells the story. In all, over the six and one-half year period, there were 83,245 treatments, one embolus to every 2,973 injections, and 8 deaths. The gradually decreasing rate of accident is interesting. In view of the fact that we were dealing almost exclusively with advanced tuberculosis, 28 accidents to 83,245 treatments compare favorably with institutionalized collapse and dispose of the contention that extramural pneumothorax, from the initial injection onward, is necessarily a hazardous undertaking. Here and now, while on the subject of embolism, may I mention that I think the type of needle is important. From the start of the program and affecting the entire organization, I have insisted that the slotted needle be used for the first four injections of induction, the sharp, 18-gauge needle for maintenance, and the slotted needle again for the later stages of reduction.

SUMMARY AND CONCLUSIONS

In 7,341 cases observed over a six and one-half year period, the results were twice as good in the treated cases as in the controls.

Undue attention must not be paid to the mortality tables as an index to the value of collapse. Collapse in widespread application is too new to affect the tables conspicuously or to dominate morbidity, the flux of summating and conflicting influences that actualizes itself in the composition of the death rates.

To be fully effective, collapse as a measure of community control should have wide-spread and efficient application. Wherever possible, the unified plan should prevail, intramural collapse, extramural collapse, reciprocity of function, interchange of patients as between the sanatorium and the field. For the fullest measure of community control this combination is necessary. Where the sanatorium ends, the field clinic, expansile, inexpensive, elastic in its applicability to the need, begins.

The much discussed question of the initial treatment outside the Sanitarium did not seem to make a very great difference, 70.6 per cent living for those who received the initial treatment in the clinic as against 78.1 per cent for the patients that received their first injection in the Sanitarium. The figures embracing 3,090 treated cases explode the

belief still current in some quarters that the induction of collapse is purely an institutional prerogative.

Owing to its possibilities in the direction of community control, collapse in the Negro deserves more energetic consideration. In the present study the results for the Negro, while not up to those for the white, are considered satisfactory. A gap in the mortality of six to one is reduced to a gap of three to two, a sequence that holds solemn implications for those entrusted with a program of control in large communities.

As a result of the investigation and of actual experience in the clinic and at the bedside, the officers and medical personnel engaged in the study are convinced that collapse, in its dual capacity as public health instrument and medium of cure, symbolizes a union of ends and aims, offering the patient his best chance and the community its best protection.

THE MANAGEMENT OF PLEURAL EFFUSIONS COMPLICATING ARTIFICIAL PNEUMOTHORAX[1,2]

T. DE CECIO AND B. P. POTTER

While we do not claim an exhaustive review of the literature, investigation of representative contributors reveals that much has been written on such phases as the incidence (6, 7, 8, 9), bacteriology (10, 13, 14, 15), chemistry (5) and prophylaxis (1, 5, 16) of pleural effusion complicating artificial pneumothorax. Realizing the existing disagreement on these questions, they will not be discussed further except in such instances where their consideration, particularly the bacteriological nature of fluids, is a significant factor in clinical management.

Excepting those instances in which superimposed infection by organisms other than tubercle bacilli occurs, there appear to be considerably varied definitions of tuberculous empyema (17, 4, 2, 5, 18). There are those who base the diagnosis of tuberculous empyema on one criterion alone—presence or absence of tubercle bacilli regardless of the type of fluid. Others are of the opinion that a fluid must be cloudy and contain tubercle bacilli before being labeled as empyematous. Still others would add to the latter, clinical manifestations such as fever and toxicity which in our experience have been found to be transient in most instances.

The differences in these concepts would, when superficially viewed, appear to be of academic interest only, were it not for the fact that the clinical management of complicating effusions is based directly upon them. We have encountered instances where surgery was advised because there was a cloudy, bacillary (tubercle bacilli) effusion despite the absence of symptoms. We have seen cases where antiseptic pleural lavage, with or without subsequent oleothorax, was resorted to in similar effusions. Some have even meddled with clear fluids because they were bacillary, in the belief that they sooner or later become empyematous.

As a result of these concepts, the occurrence of a complicating effusion

[1] From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

[2] Read before the Clinical Session of the Tuberculosis Sanatorium Conference of Metropolitan New York, February 15, 1939.

in the course of pneumothorax is regarded by many as a bad omen. Most references in the literature stress the deleterious effects of fluid; few comment on the favorable influences of effusions under certain conditions.

For the past seven years we have been particularly interested in the subject of effusions complicating the course of pneumothorax and have made careful bacteriological, experimental and clinical studies which have led to conclusions that we believe are of practical importance. The basis of the study has been the analysis of 595 cases of pneumothorax of which 203 developed fluid. However, in only 158 was the effusion a factor in the therapeutic problem. Although in all the effusion was observed clinically, fluoroscopically and/or roentgenographically, in 63 cases yielding 108 fluids correlative bacteriological and clinical studies

TABLE 1

Correlation of 63 cases of pneumothorax effusion and their initial and subsequent bacteriology

CHARACTER	NUMBER OF CASES	INITIAL		SUBSEQUENT POSITIVE	TOTAL POSITIVE	TOTAL FLUIDS EXAMINED
		Negative	Positive			
Clear	33	27	6	4	10 (31%)	46
Cloudy	16	7	9	4	13 (80%)	31
Opaque	14	8	6	5	11 (80%)	31
Totals	63	42	21	13	34 (54%)	108

were made and have served as a basis for our classification of pleural fluids.

Our studies (table 1) reveal that 54 per cent of pneumothorax effusions contain tubercle bacilli either initially or subsequently. However, when analyzed as to the type of fluid, one notes that 31 per cent of clear fluids are positive, while 80 per cent of cloudy and opaque fluids are positive. It is obvious that if one considers a positive, cloudy fluid to be a tuberculous empyema the vast majority of complicating effusions are empyemata. Such a concept is further nullified by the observation that patients presenting bacillary clear, cloudy or opaque fluid, in our experience, with certain exceptions to be mentioned later, do well and obviously differ in the course taken by those presenting clinically tuberculous empyema.

Table 2 is self-explanatory in classifying pleural fluids complicating

artificial pneumothorax. It is to be noted that the classification is predominantly a clinical one, correlated with the gross appearance of the fluid and the bacteriology. Thus, a frankly purulent bacillary (tubercle bacilli) fluid, which forms rapidly and similarly tends to reform, characterized clinically by prolonged fever with frequent remissions and

TABLE 2

Clinical classification of pleural fluids complicating artificial pneumothorax based on a bacteriological and clinical study of 100 cases

	PHYSICAL CHARACTERISTICS	CLINICAL CHARACTERISTICS
1. Clear fluid	Remaining clear, 93% Becoming cloudy, 7% Or opaque— Empyema in 2.5%	Moderate extent, 82% Fever, 75%, several days to two weeks with no exacerbations Constitutional status: affected transiently if at all; tubercle bacilli found, 31%
2. Cloudy fluid	Remaining cloudy or clearing, 60% Becoming opaque, 40% Empyema in 10%	Moderate extent, 71% Fever, 71%, two weeks to one month Constitutional status: moderately affected only during acute stage; tubercle bacilli found in 80%
3. Opaque fluid	Remaining opaque, 70% Becoming empyematous, 30%	Massive extent, 40% Fever in practica ly all Constitutional status: moderately affected but not prolonged to chronicity; tubercle bacilli found in 80%
4. Frankly purulent	Empyema	Massive extent in almost all Fever: all for months with frequent remissions and recurrences Constitutional status: progressive decline with chronicity; tubercle bacilli practically always found

recurrences, and resulting in progressive constitutional decline as chronicity is established, is in our terminology a tuberculous empyema. This type of effusion will not be discussed, because its management is predominantly surgical and has been fully considered by Coryllos (23) and others.

MANAGEMENT

When an effusion appears in the course of a therapeutic pneumothorax, before a decision as to specific management can be made, one must answer certain questions:

First: Is it desirable?
Second: Is it undesirable?
Third: Is it of incidental interest only?

The answers to these questions must be integrated with the effectiveness of the collapse and with the type of fluid according to the classification presented, when the necessary data are available. Naturally, if the effusion is of incidental interest only, its management is simply confined to observation and removal if necessary to avoid the development of pressure symptoms.

Fluid may be a welcome complication where effective collapse has not been obtained as the result of circumstances which may be favorably altered through the proper utilization of the effusion.

Fixation of the mediastinum: Not infrequently during the conduct of a pneumothorax, still in the ineffective phase, the operator may be hampered by an excessively mobile mediastinum, readily demonstrable fluoroscopically and roentgenographically when observed in the full inspiratory and full expiratory positions. Increasing the pneumothorax, under such conditions, affects the cavity little, displaces the mediastinum still more, sometimes to the point of actual herniation, and gives rise to troublesome constitutional symptoms. The occurrence of an effusion in such instances may be a fortunate event. Properly utilized, the mediastinum may be fixed in a large majority. The cardinal principles from which one must not deviate are:

1: Frequent fluoroscopy (three times weekly) so as to be certain that the mediastinum is being maintained in central position while the pneumothorax space is being preserved.
2: Depending upon adequate observation, one may have to give air, remove air or fluid or both.

Within six to eight weeks, as a result of a sclerosing mediastinal pleuritis, fixation will have occurred. Therefore, early in the course of fixation, if air refills are necessary, the quantity should be small (100 to 200 cc.) and frequent rather than larger and less frequent.

The procedure for fixation of the mediastinum in individuals developing a spontaneous effusion in the presence of a mobile mediastinum is in actuality the application of observations reported by one of us (19) in a series of 68 cases in which fixation was accomplished through the induction of an artificial pleuritis by the use of such irritants as gomenol in oil, hypertonic saline and mineral oil.

Selective collapse: At times one is confronted with the problem of undue collapse of a healthy lobe, while the diseased upper lobe though not adherent will not collapse to the desired point. Increasing the pneumothorax only collapses further the uninvolved lobe. In such instances the presence of fluid can again be utilized to advantage. The aim is to allow the lower lobe to reëxpand and to adhere to the chest wall while still maintaining the pneumothorax space over the involved area. This desideratum can be accomplished by:

1: Removing the fluid, if by its presence it prevents the desired adhesion by interposing itself between the lung and the chest wall as the lobe expands.
2: Allowing reëxpansion of the lower lobe to occur slowly through the injection of 100 to 150 cc. of air two to three times weekly.
3: Fluoroscoping frequently so as to not allow the lung to adhere beyond the desired point and so invalidate the pneumothorax completely by the development of obliterative pleuritis.

The lobe is adherent when on fluoroscopic examination it does not separate from the chest wall on full expiration. Having achieved adherence, the pneumothorax can be gradually increased but the pressures must not exceed a mean of zero until firm adhesions have been formed.

Rapid closure of cavity: All who have done any appreciable amount of pneumothoraces have observed on occasions the almost miraculous closure of a previously resistant cavity following the development of effusion. In some instances the entire lung or cavity-bearing lobe becomes unaerated. The exact mechanism of this phenomenon is still in the realm of theory. Other cases, despite the fact that aeration continues, show a more gradual but definite progressive reduction in size of a cavity which had previously resisted all efforts with uncomplicated pneumothorax. In this latter type of occurrence it is of interest to note the work of Wolfe, Wang and Van Allen (20) who showed that this might occur through the development of an invasive interlobular fibrosis from a thickening pleura.

In many cases, with the development of atelectasis, the intrapleural

pressure becomes highly negative and requires adjustment. In others, the pressure may become positive due to rapid formation of fluid requiring aspiration of the fluid. When adjustment has occurred, that is, when the intrapleural pressures are not unduly positive or negative, then maintenance is all that is necessary if the cavity has closed. If the cavity has not closed but has shown a definite reduction in size, the production of a "constant pressure"[3] pneumothorax may reward the operator with an effective collapse.

Having observed this phenomenon clinically it has been utilized by us (21) in inducing effusions artificially in selected cases. These now total 22 with closure of a previously resistant cavity in 17.

Effusions in the course of pneumothorax may be definitely unwelcome.

Obliterative pleuritis: Given an individual with a recently effective pneumothorax the development of an effusion, especially if the air space is small, may completely invalidate the therapy through the development of obliterative pleuritis.

In order that obliterative pleuritis may be detected at its inception, frequent fluoroscopy is imperative. The patient must be so tilted that the part of the lung lying beneath the fluid is clearly visualized. When one notes that the lung is creeping toward the chest cage, then obliteration is imminent. The fluid should be removed and small frequent refills should be given, daily if necessary, to maintain the intrapleural pressures at zero as a mean. If, despite these manoeuvres, reëxpansion continues to take place one may have to resort to a maintenance oleothorax. In our statistics, it was found that obliterative pleuritis was uncontrollable in only 7.6 per cent.

Adhesions: The occurrence of an effusion complicating a pneumothorax which is ineffective due to adhesions may, through thickening and occasionally subsequent shortening of the adhesions, alter the outcome of the pneumothorax. If the adhesions are noncauterizable, it is best to abandon the pneumothorax, allow reëxpansion to occur and turn to some other form of therapy, if possible.

Residual fluid: One of the sequelae of pleural effusion regarded by some with ominous forebodings is residual or recurrent effusion. This need not be so regarded, for out of a total of 184 effusions complicating pneumothorax there were 65 (35 per cent) residual effusions of which only 8

[3] In the average pneumothorax the intrapleural pressures gradually change between refills in the direction of negativity, as the air absorbs. To avoid these fluctuations, frequent refills of small to moderate quantities of air assure a more or less constant intrapleural pressure.

(12 per cent) became empyematous. The management of residual effusion depends on whether or not reëxpansion is desired. If not desired, the fluid should not be disturbed except for aspiration with air substitution from time to time in order to prevent pressure symptoms. If reëxpansion is desired, it can be hastened by "negative pressure" aspirations, a method introduced at our institution about two years ago and recently reported independently by Woodruff (22). The procedure consists of aspiration of fluid without air replacement, to the point where the patient begins to experience tightness in the chest. It is repeated once or twice weekly. As a result of this method, it has been both interesting and unexplainable to note the remarkable change in the character of the fluid. Particularly striking have been the opaque fluids which after two to three aspirations become cloudy and then clear, serofibrinous. Parallel with the reduction in the amount of fluid there has been noted a marked constitutional improvement, probably the result of decreased toxic absorption. Remarkable reëxpansion occurred in every instance in spite of thickened pleura in some. However, in the majority, reëxpansion could be accomplished only to the subtotal point. Even this has been of value, for patients who previously were not amenable to surgery because of poor constitutional status coupled with the necessary extensive surgery have had the tide turned as a result of improvement and reduction in the extent of required surgery.

Reëxpansion: Another undesirable feature of complicating effusions that one hears voiced is the difficulty in expansion of a lung after it has been collapsed for the desired period of time. In a study of 68 reëxpansion cases in our Out-Patient Department, we have brought about reinflation in all without any supplementary procedures. Twenty-four of these cases had, during the course of pneumothorax, fluids the nature of which we have discussed. It is noteworthy at this point to add that 15 of the group of cases wherein the mediastinum was fixed by oleothorax have been reëxpanded without any difficulty, except in one instance which required a supplementary phrenic interruption.

While the general management of these nonempyematous fluids, regardless of type, has been discussed with relation to the problems of pneumothorax, it is significant to note at this point a few admonitions as regards the type of fluid. As will be seen from table 3, positive fluids do present to a greater extent the dreaded complications of pneumothorax, that is, bronchopleural fistula and empyema.

It will further be recalled that 30 per cent of the opaque fluids become

true empyemata. One must carefully integrate this information with the probabilities of the collapse before definite decision can be made.

Examples: The development of an opaque, positive fluid in a patient with an ineffective collapse and a mobile mediastinum should make one lean toward abandoning the pneumothorax soon, without deliberating too long on the probabilities of effective collapse. An individual with an effective pneumothorax, maintained for the minimum desired period of time, who develops a cloudy, positive fluid should be reëxpanded and not allowed to carry the pneumothorax to the maximum period. However, if in a case of effective collapse, which has been maintained for the minimum period of time, there develops a cloudy or opaque fluid and the

TABLE 3

Comparison of clinical course of 63 cases with bacilliferous and nonbacilliferous fluids (tubercle bacilli)

	POSITIVE FLUIDS CLEAR, 10; CLOUDY, 10; OPAQUE, 14	PERSISTENTLY NEGATIVE FLUIDS CLEAR, 23; CLOUDY, 3; OPAQUE, 3
Number of cases	34	29
Complete resorption	12 (35%)	18 (62%)
Recurrent or residual fluid	22 (65%)	11 (40%)
Febrility	20 (59%)	20 (70%)
Complications:		
Bronchopleural fistula	10 (30%)	1 (3.4%)
Empyema	10 (30%)	0
Management:		
Aspiration	34 (100%)	29 (100%)
Tube drainage	6 (19%)	0
Thoracoplasty	1 (3%)	0

operator is very solicitous of maintaining the collapse as long as possible, the decision becomes a delicate one but may be safely made. Remembering that 90 per cent of cloudy fluids and 70 per cent of opaque fluids run an uneventful course, the operator may choose to watch the individual carefully, while still maintaining the collapse, and with the first suggestive signs of empyema abandon the pneumothorax. Or, the preferable procedure in our experience has been substitution oleothorax.

In conclusion, in defining nonempyematous effusions there has been presented a classification of pleural fluids in tuberculosis based on bacteriological and clinical studies. Furthermore, the management of these effusions has been presented from the standpoint of their rôle as

factors in the conduct of pneumothorax, stressing both favorable and unfavorable influences of pleural effusions.

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TRANSMEDIASTINAL HERNIA[1]

Mediastinal Movements during Respiration in Bilateral Pneumothorax

MAX FINKELSTEIN

Transmediastinal pleural hernia occurring during the course of unilateral pneumothorax is a condition commonly observed on X-ray films of the chest and by fluoroscopy. There are two sites where such hernias are prone to occur. One is situated anteriorly, in the superior mediastinum. At this point, the hernia pushes its way through the mediastinum directly behind the manubrium and the upper part of the body of the sternum. In this situation, a hernia may occur with equal facility when it arises either from the right or from the left side. The second site of predilection is situated in the posterior mediastinum, inferiorly. Here, the hernia occurs between the aorta and the oesophagus. Almost always, hernias situated here arise from the right side of the chest.

In many patients receiving unilateral pneumothorax, the heart, mediastinum (and hernia, when present) go through side-to-side movements during respiration. In the large majority of cases, these structures may be seen moving toward the side of the pneumothorax (and therefore toward the side from which the hernia arises) during inspiration, and away from the side of the pneumothorax during expiration. As a result, a transmediastinal pleural hernia is usually largest and most prominent at the end of expiration, and least conspicuous at the end of inspiration. In some cases the hernia cannot be seen at all at the end of inspiration.

Although transmediastinal pleural hernia is quite common in cases receiving unilateral artificial pneumothorax, it has been very infrequently reported in bilateral artificial pneumothorax. We have been able to find 6 such cases in the literature. The first was reported by Cantieri (1) in 1925. Subsequently, single cases have been reported by Bordet and Parodi (2), Locatelli (3), Raimondi and Sangiovanni (4), Timpano (5), and Rey, Rey and Pucci (6). The English and American literature seem to be entirely bare of references to this condition.

[1] From the Medical Department of the National Jewish Hospital, Dr. Charles J. Kaufman, Medical Director, Denver, Colorado.

It has been our good fortune to discover 3 such cases, brief reports of which are given below.

CASE REPORTS

Case 1: M. G., female, 19 years old, admitted October 11, 1936. There was a history of illness dating back five years. X-ray of the chest revealed bilateral pulmonary tuberculosis, about equally extensive on each side. There was

TABLE 1

CASE NUMBER	BEFORE REFILL INTRAPLEURAL PRESSURES				REFILL	AFTER REFILL INTRAPLEURAL PRESSURES			
	Right		Left			Right		Left	
	Inspiration	Expiration	Inspiration	Expiration		Inspiration	Expiration	Inspiration	Expiration
1	−1	−6	−4	−8	400 cc. left side	−1	−8	−1	−6
	Hernia visible arising from right side					Hernia not visible			
2	−3	−8	−3	−9	350 cc. right side	0	−4	−3	−5
	Hernia visible arising from right side					No change in appearance of hernia			
3	+6	−7	+2	−11	150 cc. right side	+8	−4	+3	−13
	Hernia visible arising from right side					No change in appearance of hernia			
3	+3	−7	+3	−12	200 cc. left side	+3	−8	+9	−6
	Hernia visible arising from right side					No change in appearance of hernia			

also a severe tuberculous involvement of the pharynx, fauces and tonsils. Artificial pneumothorax was begun on the left on December 24, 1936. The intrapleural pressures were always negative. On May 13, 1937 artificial pneumothorax was begun on the right, and maintained subsequently under negative pressures. On August 11, 1937 a transmediastinal pleural hernia was noted during a fluoroscopic examination. The hernia arose from the right side of the chest, and was situated in the anterosuperior mediastinum. There were no symptoms that could be ascribed to this hernia, and no signs

by means of which its presence could be ascertained. On fluoroscopy, it was seen to move from side to side with respiration. During inspiration, its border moved further to the left; during expiration, it moved back toward the right side. The heart and mediastinum went through side-to-side movements, synchronously with the hernia. The direction of motion was, as for the hernia, to the left during inspiration, and back toward the right during expiration. On August 16, 1937 intrapleural readings were taken immediately after the hernia had been visualized by fluoroscopy. The intrapleural pressures at this time, both before and after a refill on the left, are given in table 1. The patient was fluoroscoped immediately after the refill. The hernia could not be seen, either in expiration or in inspiration. Subsequently, the hernia reappeared, and persisted up to the time of the patient's death of miliary tuberculosis. Although fluid developed on the left side, negative intrapleural pressures persisted, and the hernia remained visible. Inspiration-expiration films taken during this time show the movements of the hernia, the heart, and the mediastinum with respiration (figures 1a and 1b).

Case 2: P. H., female, 15 years old, admitted November 27, 1936. There was a history of illness dating back one year. X-ray films of the chest revealed far advanced pulmonary tuberculosis, occupying a large area of the left lung field, but with a large cavity at the right apex. Artificial pneumothorax was begun on the right on October 12, 1937, and maintained with negative intrapleural pressures. No hernia was seen while unilateral pneumothorax was being continued. Pneumothorax was induced on the left on January 6, 1938; it was maintained under negative intrapleural pressures. On January 8, 1938, a transmediastinal pleural hernia was discovered on an X-ray film of the chest. There were no symptoms ascribable to this hernia, and no physical findings by means of which its presence could be determined. The hernia arose from the right hemithorax, crossed the mediastinum behind the manubrium and upper part of the body of the sternum, and appeared to the left of the aortic knob. Fluoroscopy established its position in the anterosuperior mediastinum. It was also noted that during inspiration the border of the hernia moved to the left; on expiration, it moved to the right (figures 2a and 2b) and at times became lost in the mediastinal shadow. This was confirmed many times. The heart and mediastinum moved very little with respiration. On a few occasions, a slight shift to the left was noted with inspiration, and to the right with expiration. During many subsequent fluoroscopies, the hernia was visible on some occasions, and not seen on others. On March 24, 1938, following a refill on the left, it was not visible; the next day, following a refill on the right, it was seen once more. Another time, after no air had been given on the left for ten days, the hernia was seen clearly; one week later, after two refills had been given on the left, it had apparently disappeared. Simultaneous intra-

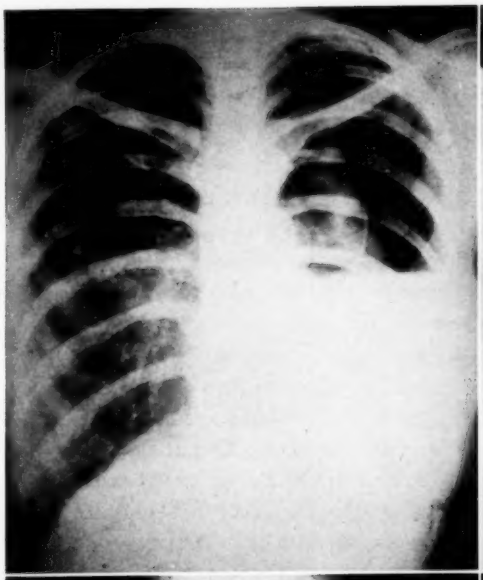

FIG. 1a

FIG.

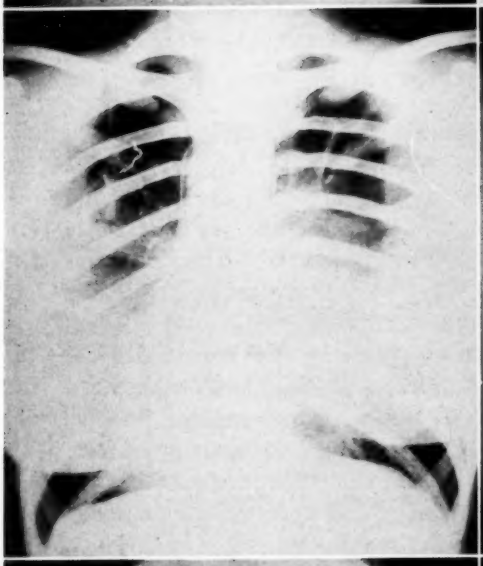

FIG. 2a

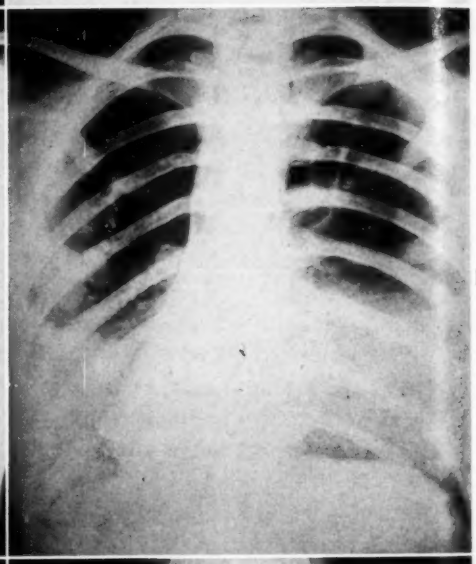

FIG.

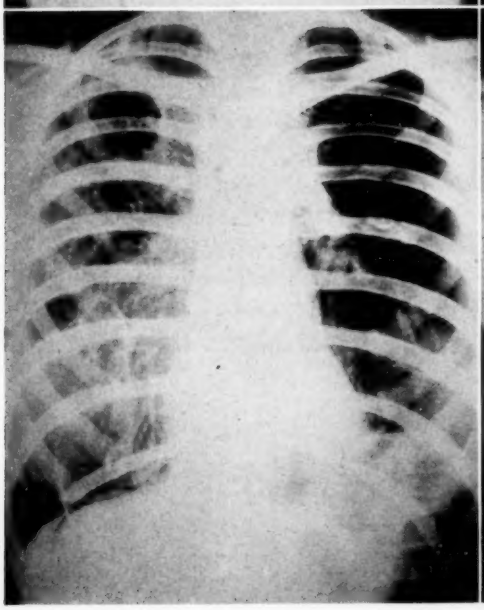

FIG. 3a

FIG.

FIGS. 1a–3b

pleural pressures were taken on each side on November 3, 1938, when the hernia could be seen on fluoroscopy. The intrapleural pressures at this time, both before and after a refill on the right side, are given in table 1. There was little change in the appearance of the hernia after the refill.

Case 3: B. E., female, 28 years old, admitted on January 14, 1935. Her illness began fourteen years before. A left phrenicectomy had been performed early in 1934. On admission X-ray films revealed bilateral pulmonary tuberculosis, more extensive on the left. The left diaphragm was elevated and apparently paralyzed. This paralysis persisted throughout the period of observation. Pneumothorax was begun on the right on December 31, 1935. The intrapleural pressures were at first negative, later positive during expiration. No hernia was noted while unilateral pneumothorax was being maintained. On April 28, 1936, pneumothorax was begun on the left. In November of that year, fluid appeared on the left side. This absorbed spontaneously. Positive pressures were found during the presence of the fluid, and for some time after its absorption. In August, 1938 a transmediastinal pleural hernia was noted, arising from the right side. The hernia was completely asymptomatic, and there were no signs by means of which its presence could be ascertained. There was no fluid in the left hemithorax at that time, and the intrapleural pressures were slightly positive during expiration and highly negative during inspiration. In November, 1938 the hernia was noted on fluoroscopy. On inspiration, its border was seen to move to the left, and on expiration back to the right. It appeared considerably smaller during expiration. The heart and mediastinum moved in the same direction as the hernia during inspiration

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FIG. 1a. Case 1. Inspiration film. Note the position of the right border of the heart and of the hernia. The margin of the latter is an appreciable distance to the left of the crossing of the shadows of the second rib anteriorly and the seventh rib posteriorly.

FIG. 1b. Case 1. Expiration film, taken immediately after 1a. The heart has shifted to the right, as has the margin of the hernia. The latter is now at about the midpoint of the superimposed shadows of the second rib anteriorly and the seventh rib posteriorly.

FIG. 2a. Case 2. Film of chest in deep inspiration, and in anteroposterior position. The hernia can be seen to the left of the aortic knob.

FIG. 2b. Case 2. Film of chest in expiration, and in anteroposterior position, taken immediately after film shown in fig. 2a. The hernia is lost in the mediastinal shadow. There is a slight shift of the mediastinum to the right.

FIG. 3a. Case 3. Film of chest in inspiration. Note the position of the border of the hernia in relation to the anterior end of the left third rib, and the position of the left and right cardiac borders.

FIG. 3b. Case 3. Film of chest in expiration, taken immediately after film shown in fig. 3a. The border of the hernia has moved to the right, leaving a considerable space between itself and the anterior end of the left third rib. The heart and mediastinum have also moved to the right, uncovering the shadows of the transverse processes on the left, and covering those on the right.

and expiration (figures 3a and 3b). Fluoroscopic examination revealed also that the hernia was situated in the anterior mediastinum, close to the anterior chest wall. Intrapleural pressures were taken simultaneously on the right and left sides on two occasions when the hernia could be seen by fluoroscopy. Table 1 records these pressures, taken both before and after a refill on each side. There was no change in the appearance of the hernia after the refill, on either occasion, in spite of the fact that after the refill on the left there was a change in the side having the lower pressure.

DISCUSSION

The majority of patients showing this condition were quite young at the time the hernia was discovered. Among our own cases and those taken from the literature, 5 were in their teens, 2 in the early twenties and only one had reached the age of thirty. Five of the cases were females, 2 males; in 2 the sex was not stated. The duration of illness before the discovery of the hernia was one year or less in 4 cases, two years in 2 cases, six years and seventeen years respectively in the remaining 2 cases. The hernia arose from the right side in 6 instances, and from the left side in 2; in one case there was herniation of each pleural sac into the opposite side (Locatelli, (3)). Locatelli's case had three hernias: a right to left anterior-superior hernia, a left to right anterosuperior hernia, and a left to right posteroinferior hernia. A double hernia, both sacs arising from the right side, was reported by Raimondi and Sangiovanni (4). One hernia was in the anterosuperior, the other in the posteroinferior mediastinum.

In 6 cases the right side was the first collapsed. Among these cases, the hernia arose from the right side three times, and from the left side twice; in one case (3) bilateral hernias were present. In 2 instances, left pneumothorax preceded the right; the hernia arose from the right side in both these cases.

In our own cases, and in those reported cases which we could check up adequately, a free pleural space was found on each side, with only a few isolated adhesions. During the course of treatment, 2 of our cases developed effusions, yet the hernias occurred and the mediastinum, in each case, continued to show considerable mobility. These facts would seem to point to a failure in the production of thickening and fibrosis in the pleura and mediastinum of these individuals, in spite of conditions that ordinarily favor such processes. Whether this is due to a peculiarity in the patients, or to the character of the disease, it is impossible to state. As for the influence of this peculiarity on the outcome of the disease, one

of our patients died of miliary tuberculosis, and 2 are living and seem to be doing very well.

In 2 instances of those reported here, and in another (1) from the literature in which the hernia arose from the right side, pneumothorax was first induced on the right, but no hernia was seen until a bilateral pneumothorax had been established. This seems difficult to explain, unless we assume that, due to the bilateral pneumothorax, there was an increase in the anteroposterior dimension of the chest, and a consequent enlargement of the "weak spot" usually present between the sternum and the solid tissues of the upper mediastinum. Another possibility is that the contralateral pneumothorax aided in producing the hernia by removing the support offered the "weak spot" by the uncollapsed contralateral lung.

In all 3 of our cases the hernia arose from the right side. The factors possibly causing this may be seen by a comparison of the intrapleural pressures on each side, taken simultaneously on the left and right in cases 2 and 3, and one after the other in case 1 (table 1). It will be seen that in each case the pressures on the left were lower, before air was given on any particular day, than the pressures on the right. The hernia was distinctly visible each time these pressures were taken. In case 1, following a refill on the left, the lower pressures were present on the right; the hernia, previously present, could not be seen following this refill. In case 2, following a period of ten days during which no air was given on the left, the hernia was very clearly seen; one week later, after two refills on the left, it was no longer visible. Such clear cut behavior of the hernia with changes in intrapleural pressures seems to afford strong evidence that the hernia is due to differences in intrapleural pressures between the right and left sides. Case 3 does not completely bear out this hypothesis, since a change in the side having the lower pressures did not result in any demonstrable change in the hernia. This does not invalidate the theory completely, for it seems quite likely that a hernia may not respond immediately to changes in intrapleural pressures, yet might respond to long continued and constantly applied force due to the differences in intrapleural pressures in the long intervals between refills.

The lateral movements, during the respiratory cycle, of the heart, mediastinum and hernia in each of the cases here presented were in a direction opposite to that commonly observed in cases of unilateral pneumothorax. During expiration the hernia was seen, in all cases, to

move toward the right side, the side from which it arose; during inspiration, the hernial border moved back to the left. The hernia was most prominent at the end of inspiration, being invisible at times at the end of expiration. The heart and mediastinum moved synchronously with the hernia, and in the same direction as the hernia, during each phase of respiration.

In seeking an explanation for this peculiar phenomenon, which was noted also in a number of the cases described in the literature, one is led first to the differences in pressure between the right and the left sides of the chest. However, a study of our own simultaneous pressure readings leads to the conclusion that the shift of the mediastinal structures cannot be explained on this basis. The difference between the intrapleural pressures, during inspiration, is sometimes greater than during expiration, but just as often it is not as great. It seems evident that the mediastinum and its contents are subject to forces that are not reflected in the intrapleural pressures. The forces responsible for the observed movements may be the respiratory muscles, but it is difficult to see how these muscles can act directly to produce the observed phenomena. Another force which must be considered is that due to the expanding lungs. This is a result of the action of the muscles of respiration, but is produced directly by the atmospheric pressure acting through the lung. It is our belief that it is this last force which causes the displacement of the heart, mediastinum and hernia to one side or the other.

In considering the entire problem of mediastinal shift during respiration, one becomes aware of the fact that in all conditions exhibiting such shift there is reason to believe that one lung expands and contracts more fully than the other. Such is the case in unilateral pneumothorax and in massive atelectasis. In these conditions, it is common to observe mediastinal displacement, directed away from the involved lung during expiration, and toward the involved lung during inspiration. In both conditions, it is the uninvolved lung that expands and contracts more fully and completely. It may be said, therefore, that the mediastinum shifts away from the better expanding lung during inspiration, and toward the better collapsing lung during expiration.

A study of the chest films of the cases here reported has convinced us that in each case the right lung expanded to a greater degree, during inspiration, than the left lung. The movements of the heart, mediastinum and hernia were so directed that, during inspiration, these structures moved away from the side containing the better expanding lung.

During expiration, the right lung emptied better than the left, and at the end of expiration the right lung occupied a smaller volume, compared to its inspiratory state, than the left lung. The mediastinal structures, during expiration, were displaced toward the side containing the more actively collapsing lung. These observations indicate that, in bilateral pneumothorax, mediastinal shift during respiration is due to the same causes as when it occurs in other conditions. The enlargement of the hernia during inspiration is probably due to the gas displaced by the rapidly expanding lung, which is forced into and further distends the hernial sac. Some of this enlargement is, however, apparent rather than real, as the hernial border is carried along with the mediastinum as a whole.

It would seem, therefore, that there is some reason to ascribe mediastinal shift during respiration to unequal expansion and contraction of the lungs. It seemed desirable to subject this hypothesis to experimental trial. In order to do this an air-tight chamber was constructed and separated into two chambers by a flexible rubber partition. The movements of this partition could be observed through the glass walls of the chambers. In each chamber there was suspended a rubber balloon, the inside of which was open to atmospheric pressure. Both chambers were connected by a common tube to a water pump, by means of which a considerable degree of reduction in pressure could be produced and maintained. In addition, each chamber was connected to a water manometer graduated in centimeters, similar to the manometers commonly used in artificial pneumothorax treatments.

The balloons were chosen so that one expanded more readily than the other. As a result, when a certain reduction in pressure was secured in the air-tight chambers, one balloon expanded considerably more than the other, even though the pressures in both chambers were identical. When this occurred, the flexible partition would begin to bow out into the opposite chamber. This bowing continued as long as one balloon continued to expand at a more rapid rate than the other. If this expansion was stopped (as could be done by closing off the rubber tube connecting the inside of the balloon with the outside air) the movement of the partition was arrested at whatever point it had reached. If the other balloon was made to expand at a more rapid rate than the first balloon, the direction of displacement of the partition was promptly reversed.

By admitting atmospheric pressure into the air-tight chambers after one balloon had achieved a greater degree of expansion than the other,

both balloons were permitted to collapse. The balloon that had expanded more collapsed to a greater degree than the other, compared to its inflated state. Invariably, the partition moved toward the side containing the better collapsing balloon, as deflation occurred. By controlling the speed of deflation of each balloon (as by closing off the rubber tube through which the air in the balloon escaped) the partition could be made to shift to one side or the other, always moving toward the balloon undergoing the greater deflation at the time. When it was arranged that each balloon collapsed at about the same rate, the partition showed little or no deviation to one side or the other.

The movements of the partition occurred without there being any actual contact between the expanding balloons and the partition. During the time that one balloon was expanding more than the other, and the partition was moving to one side, the pressures in the two chambers were always identical. The displacement of the partition appears to be the mechanism by which this equality of pressures is maintained. During deflation, it was found that the pressure on the side containing the balloon undergoing greater collapse tended to be lower than the pressure in the other chamber. If the speed of deflation was slowed down, the pressures could be kept almost equal. Nevertheless, the partition continued to move toward the balloon undergoing the greater collapse, although the movement was not as marked as when rapid deflation was permitted.

These experiments confirm the hypothesis that mediastinal shift during respiration is due to unequal inflation and deflation of the two lungs. The system described may be fairly compared to the pleuropulmonary system, the principal difference being that in the latter a negative pressure is produced by the expansion of the walls of the airtight chambers, whereas in the artificial system the walls are fixed, and the negative pressure is produced by a pump. In each system, however, there are two elastic bags, open to the air, which are alternately inflated by the atmospheric pressure as the pressure outside the bags drops, and allowed to collapse by their own elastic tension as the pressure outside them again approaches or reaches atmospheric. It may fairly be assumed that the effect on the partition between the chambers (in the chest, the mediastinum) is the same, no matter how the negative pressure is produced.

SUMMARY

1. Three cases of bilateral pneumothorax exhibiting transmediastinal pleural hernia are presented.

2. In each case, the hernia was asymptomatic, and the discovery was made by means of X-ray films or fluoroscopy of the chest.

3. The subjects were all young women in whom the disease began during adolescence.

4. The hernia arose from the right side in each case, and was situated in the anterosuperior mediastinum.

5. In all 3 cases, the hernia, heart and mediastinum moved away from the side of origin of the hernia during inspiration, and toward that side during expiration.

6. It seems likely that the occurrence of such a hernia is due to the following circumstances:

(a) Presence of the usual "weak spot" in the upper mediastinum,
(b) Lack of fibrosis in the pleura and mediastinum,
(c) Differences between the right and left intrapleural pressures, maintained for a considerable time.

7. The direction of movement of the heart, mediastinum and hernia, during the respiratory cycle, is probably due to differences in the degree of expansion and deflation of the two lungs. During inspiration, the mediastinum is displaced away from the better expanding lung; during expiration, it moves toward the lung undergoing greater deflation.

8. The validity of this explanation is confirmed by experimental evidence obtained through the use of an artificial pleuropulmonary system.

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PRECURSORS OF FORLANINI AND MURPHY

LOUIS R. DAVIDSON,[1] MURRAY FUHRMAN[2] AND VINCENT J. RELLA[2]

That artificial pneumothorax has come to stay in modern therapeusis is no longer a doubtful premise. In the hands of competent men, fully cognizant of the possibilities and the limitations of this procedure, and with the development of modern pneumothorax inducing machines, the fears of those, who in former years strongly advised against artificially induced pneumothorax therapy, have gradually disappeared. To-day it is practiced the world over.

It is clearly recognized that Carlo Forlanini and J. B. Murphy deserve full credit for the development of artificially induced pneumothorax as it is practiced to-day. Yet, that the work of their precursors played an important rôle in the evolution of the concept of this therapeutic procedure is not at all fully appreciated.

Before proceeding to the main theme of this article, the evolution of the modern pneumothorax apparatus, it would be well to review the work done by the predecessors of Forlanini and Murphy and to give them credit for that which rightfully is theirs.

Phthisiologists are fairly well acquainted with Forlanini's original communication on artificial pneumothorax. This work first appeared in August, 1882, in an Italian medical journal (1). In this publication, on purely theoretical grounds, the author advanced the belief that artificially induced pneumothorax might be employed as a therapeutic measure in the control of pulmonary tuberculosis. Intimately conversant with Toussaint's work (2) which appeared two years previously, on the beneficial influence that a spontaneous pneumothorax may exert on the underlying pulmonary lesion, Forlanini reasoned that a similar favorable influence might be produced by an artificially induced pneumothorax. For twelve years, therefore, he experimented with this premise, despite the indifference and skepticism of his colleagues and not until 1894 did he present his *First Attempts at Artificial Pneumothorax in Pulmonary Phthisis* (3) (at the 11th Medical Congress in Rome). The

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following year he was able to report the *First Case of Pulmonary Phthisis, Unilateral and Advanced, Successfully Cured by Artificial Pneumothorax* (4).

The medical world paid little attention to Forlanini's classical work and it was not until the appearance of Murphy's paper on *Surgery of the Lung* (5), presented at an American Medical Association meeting in 1898, that the profession began to admit possibilities in this new therapeutic procedure. Murphy makes no mention of Forlanini's work[3] and we must therefore assume that he arrived at his conviction independently that the use of an artificially induced pneumothorax to collapse a phthisical lung "is the keynote to the successful treatment of pulmonary cavities" (6).[4]

First, however, let us review the rôle played by the forerunners of these two men and see how they implanted the seeds for the development of artificial pneumothorax therapy. Forlanini's concept of this principle occurred to him as a theoretical premise—a premise arrived at by several observers previously, both on experimental and clinical grounds. Before artificial pneumothorax could be adopted as a therapeutic procedure, it had to be firmly established:

1: That paracentesis of the chest is not a dangerous procedure
2: That air, *per se*, in the pleural cavity, is harmless
3: That the introduction of air into the pleural cavity leads to collapse of the lung
4: That collapse of the lung so produced may exert a beneficial influence

Recognition, as precursors of Forlanini and Murphy, must go to the pioneers who helped to establish these vital facts.

Hippocrates (460–370 B. C.), in his second book on affections, speaks of the treatment of empyema resulting from chest wounds by inserting a tube into the pleurocutaneous fistula, attaching a bladder to it and delivering air into the pleural cavity. Hippocrates may possibly have inferred that the introduction of air leads to collapse of the lung and favors the healing of pulmonary wounds (as Young (7), Krause (8) and others believed), but the weight of scholarly opinion (9) is that the

[3] Forlanini's work is listed in the Index Catalogue of the Surgeon General's Office, United States Army, under *Phthysis*, and the reference was available to anyone who sought it.

[4] Murphy, though firmly convinced of the value of artificial pneumothorax therapy, was reluctant to practice the method himself, for he felt that by doing so he would tend to drift from pure surgery into the realm of medicine.

air was introduced to drive the pus to the exterior and to drain more efficiently the pleural cavity.[5]

Plato (429–347 B. C.) tells of Euriphon de Cnide who saved the life of the dying Cinesiasi by opening his chest through means of a hot iron (10).

Bontius (1658) and Bartholin (1616–1680) report the treatment of empyema by incising into the chest and introducing antiseptics into the pleural cavity (10).

Purmann (11), in the 17th century, though realizing that deep chest wounds involving the lungs are dangerous, pointed out that they are not always fatal and that the entrance of air may not cause much disturbance. He cites two cases which recovered completely following the establishment of adequate drainage after having received deep, penetrating thoracic wounds.

Baglivi (12), in 1696, described the cure of pulmonary tuberculosis following chest wounds received in battle. This author—the first to do so—advocated opening the thorax and introducing medicaments directly into the diseased lung for the treatment of pulmonary phthisis. It is quite possible that the beneficial results which ensued here may have been produced by the unintentional establishment of a pneumothorax.

Barry (13), at a later date, realized that a "difficulty which often prevents healing of an ulcer in the lungs is the want of sufficient rest in an organ successively enlarged and contracted," and was "well convinced that ulcers in the lungs, except for some small ones in the bronchial glands, are never cured by internal medicines, unless confined and kept more in a state of rest by such an adhesion."[6] He advocated opening into the chest and into the pulmonary abscess. He cites several cases which recovered or improved following this procedure. However, it is very likely that a number of his cases were simple pyogenic empyemata and that these showed the expected improvement following paracentesis and the establishment of drainage.

The discovery of the stethoscope and its use in localizing pulmonary cavities gave the surgical treatment of these lesions an added impetus and this procedure became quite fashionable during the 19th century shortly after the appearance of Laennec's classical work on *Mediate Auscultation* (14).

[5] P. Krause investigated this point in great detail and we recommend perusal of his analysis of the original quotations.

[6] See page 346 of Barry's work.

Mistal (10) mentions Boerhave, Ponteau, David and Sharp as having treated pulmonary tuberculosis by incising into the chest. Faye, followed by Bell and Richter at a later date, proceeded to open the chest and to inject medicaments directly into phthisical cavities. Bouchet and Brichteau made similar efforts to treat phthisis surgically. Krimer, favorably impressed by these efforts, stated in 1829 that it was possible to cure pulmonary tuberculosis by surgical intervention.

Carson (15), having failed in his attempt to establish an open artificial pneumothorax, endeavored to incise directly into pulmonary cavities.[7]

Ramadge (16), in 1834, reported 3 cases of consumption cured by paracentesis. He attempted to remove air from phthisical cavities by perforating the cavity through the medium of a trocar. His intention was to remove the air from the cavity, thereby collapsing it, and to hope for a compensatory expansion of the lower lobe. In one case, the puncture was made at a level an interspace lower than recommended, and it was noted that very little pus escaped, but that a quantity of air issued with a hissing noise. It is possible that this hissing noise was actually caused by in-rushing air and that we are dealing with a case of inadvertently established pneumothorax.

Hastings and Storks (17) and Hock (18) comment on the beneficial results which followed upon the introduction of a trocar into a phthisical cavity in a case which they observed. Air was noticed issuing through the cannula. Von Herff and Hocken reported good results following a similar surgical effort (19).

Nasse (20) insisted that you cannot cure phthisis by opening into a tuberculous cavity but felt that some mitigation of suffering might result. He stressed the importance of the presence of adhesions so that the contents of the cavity would escape to the exterior and not into the pleural sac. Nasse recognized that a hydropneumothorax might follow but unfortunately did not realize that this occurrence may exert a beneficial effect.[8] Similar surgical efforts to treat pulmonary cavities were made by Fenger and Hollister (21), Sutton, Bull, Albert and others (22).

Mosler (23) introduced antiseptics directly into tuberculous and bronchiectatic cavities via a cannula which he insinuated through the chest wall. Pepper (24) criticized this practice and advocated the use

[7] Carson's pioneer efforts will be discussed later at length.

[8] Nasse made multiple needle punctures into the chest of experimental animals and showed that the procedure was harmless and demonstrated at autopsy the formation of adhesions by this procedure.

of a long, delicate needle instead of a trocar and cannula. After numerous injections made into the lungs of healthy rabbits, he showed that the method was "practically free from all danger or serious inconvenience." He then turned to human subjects and reported beneficial results from the introduction of antiseptics (iodine and carbolic acid solution) into tuberculous cavities.

These efforts to treat tuberculous cavities locally demonstrate clearly that paracentesis of the chest is not a dangerous procedure and it is quite likely that these endeavors occasionally led to the unintentional establishment of artificial pneumothorax which may possibly account for the beneficial effects noted in several instances. Forlanini knew of these surgical attempts and it is not improbable that they played their part in influencing him to propose and attempt artificial pneumothorax therapy.

A further step was made when a number of observers undertook the experimental instillation of air in the pleural sac. Their researches provide answers to several questions of vital importance:

Is the introduction of air into the pleural cavity a dangerous procedure?
What effect will the air so introduced have?
Does collapse of the lung necessarily follow?
Does this endanger life or have serious consequences?

In a series of illuminating essays, Carson (15) revealed the results of his experimental investigations on respiration. Using different animals for his researches, including the dog, cat, sheep and rabbit, Carson induced open pneumothorax by incising into the pleura. After completing his investigations, he writes: ". . .one lung may be completely collapsed without much apparent inconvenience to the animal. I found by some experiments which I made on animals some years ago that the air may be admitted freely upon the lung of one side, without the destruction of life, and indeed with perfect safety."[9] Carson fully realized the possible clinical application of his findings, as will be later shown, and urged the trial of open artificial pneumothorax as a therapeutic measure for pulmonary tuberculosis.

Hewson (25), in 1767, published his experimental researches undertaken to demonstrate the value of *paracentesis thoracis* in threatened suffocation following spontaneous pneumothorax. He induced artificial

[9] Carson: *An Inquiry into the Causes of Respiration*, page 40.

pneumothorax in the rabbit and the dog by opening into the pleural cavity and blowing in air. In one experiment he took special care not to injure the lung, noted the immediate effects of air in the pleural space and after allowing the excess air to escape externally he states: "The animal recovered and seemed not the worse for the operation."[10]

Malgaigne (26), desirous of knowing what effect air in the pleural cavity had, showed in a series of animal experimentations that pleurisy does not result after injecting air into the pleural space. He concluded in 1842 that air, *per se*, does not have an injurious effect. He showed that the dog readily tolerates unilateral open pneumothorax but quickly succumbs to simultaneous bilateral pneumothorax. The findings were confirmed by Wintrich (27) who showed that, except for hydrogen sulphide, no gas in the pleural cavity is harmful and that inflammation and pleurisy do not follow. Szupak (28), at a later date, added further confirmation that sterile air is harmless and not inflammatory when introduced into the pleural cavity. Working on dogs, he made an incision almost to the pleura, introduced a cannula and injected air by means of a syringe.

Another important step was made when experimentation dispelled the belief that a cohesive force exists between the visceral and parietal pleura. The above investigators clearly showed that under ordinary circumstances air introduced into the pleural sac leads to a collapse of the lung. Northrup (27) demonstrated that opening the pleura by a pinhole leads to an immediate collapse of the lung. Schede (27) confirmed this and showed in his rabbit experimentations that the finest needle would cause collapse of the lung.

Weil (29), chiefly concerned with the investigation of intrapleural pressures, induced pneumothorax in dogs and rabbits, using a surprisingly modern apparatus.[11]

Davy (30), in 1823, published his observations on the absorption of gases introduced into the pleural cavity of dogs. He used a simple bellows to force different gases into the pleural space. After collapsing the lung in this manner, he notes that the health of the dog was very

[10] Page 296 of the *Works of William Hewson*. Hewson observed that, in chest wounds involving the bronchi, air escapes, causing compression of the affected lung. The term "pneumothorax" is used for the first time in his paper.

[11] Picture of Weil's apparatus appears on page 5 of *Zur Lehre vom Pneumothorax*, Arch. von Klin. Med., December 10, 1879, vol. 25; also in his *Zur Lehre vom Pneumothorax*, Leipzig, Vogel, 1882.

little impaired by the operation. He further adds, after repeating the procedure on the other side, that "this operation had very little more effect than the former."[12]

That collapse of the lung by the presence of air in the pleural sac may exert a beneficial influence was recognized by many observers who must therefore be regarded as predecessors of Forlanini and Murphy.

Baglivi (12), as is mentioned above, at the close of the 17th century, reported cases of phthisis cured by receiving chest wounds. He did not, however, consider the possibility of a traumatic pneumothorax.

Nettie presented a thesis in 1766[13] showing the beneficial effect that open pneumothorax may exert on a pulmonary wound. He knew the value of rest as a therapeutic weapon and maintained that collapsing the lung by the establishment of a pneumothorax would diminish the function of the lung, keep the organ at rest and thus approximate the edges of the wound and favor healing. Here then we have a clear exposition of the effectiveness of collapse therapy and a lucid understanding of the physiological principle involved.

At a later date John Bell similarly recognized the favorable effect that collapse of the lung has on the healing of pulmonary wounds. He states: "If the lungs when wounded were to continue in perpetual motion, I do not know how we should expect a cure . . . as the wounded lung lies in a collapsed state the edges of the wound are in contact with each other . . . thus in two days the wound heals."[14]

Young (7), in 1815, commenting on the Hippocratic practice of inflating the chest with air states "however extraordinary the practice appears, it is not impossible that it might be beneficial where the adhesion was not such as to prevent the collapse of the lung, allowing the wounded parts to reunite more readily than in the natural process of respiration, since they would be more intimately in contact with each other." He then unfortunately adds "though not more at rest."[15]

Impressed by the tendency to cicatrize which he observed in a fatal case of a penetrating chest wound, Chassaignac (10) (1835) advocated the insufflation of air into the pleural sac. He reasoned that the collapsing of the lung would cut off its blood supply and put the organ at rest.

[12] On page 502 of Philosoph. Transactions, 1823.

[13] Journal économique, 1766, page 422, quoted by Mistal (10).

[14] Quoted by Emerson (27), page 18. John Bell: *The Principles of Surgery*, edited by Chas. Bell, 1826.

[15] Page 117 of *A Treatise on Consumptive Diseases.*

Relieving the lung of its physiological function, he argued, would cure the pulmonary wound.

Boudens (10) (1836) describes a treatment of lung wounds by insufflating air into the chest to put the lung at rest. He used a pump to introduce air into the pleural cavity. Boudens refers to Ducret, a surgeon from Brest, who performed an open artificial penumothorax to arrest a haemorrhage following a pulmonary wound. Collapse of the lung, he reasoned, would compress the blood vessels and so slow down the pulmonary circulation.

Parola (10) (1849) advocated insufflation of air into the pleural sac, not only for pulmonary wounds but also to arrest pathological processes in the lung including tuberculosis. He appears to be aware of possible complications which may follow this mode of treatment—the formation of pleural exudates and empyemata.

Roser (10), in the middle of the 19th century, practiced open pneumothorax as a routine to drain purulent pleural effusions. Bartels and Quincke, at a later date, resorted to the Hippocratic method of insufflating air to evacuate empyemata more efficiently.

Despite these advances the ground was not as yet sufficiently prepared for artificial pneumothorax therapy. Further work remained to be done.

In the article on phthisis, Dictionaire des sciences médicales, published in 1820,[16] refers to Gilchrist's idea of healing pulmonary ulcers by opening into the diseased side of the chest and collapsing the affected lung. Gilchrist's original work (32), however, makes no reference to this therapeutic measure. Credit for this conception (33) must go, therefore, to his translator, Bourru[17] who took the liberty of adding notes which do not exist in the original work. Bourru referred to movements of the lung as preventing the cicatrization and healing of tuberculous ulcerations and stated that when only one lung is affected the organ can be put at rest by making an opening into the chest and permitting air to enter into the pleural cavity. This, he pointed out, would lead to collapse of the lung and put the organ at rest, thereby favoring healing of the tuberculous lesion.

We now turn to Carson (15, 34, 35) again. Having demonstrated the feasibility of artificially induced open pneumothorax on experimental

[16] Page 140 of the article on phthisis, Dictionaire des sciences médicales, Tome XLII, Mayguer, 1820. Quoted by Albert-Weil (31).

[17] French translation of Gilchrist's *Sea Voyages*, Bourru, 1 vol. Didot, Paris, 1770.

animals he reasoned "that the knowledge of this might be applied to the cure or relief of some diseases, particularly consumption."[18] "It appeared to be practicable to remove those two causes of the impediment to the cure of wounds (i.e. elasticity of the lung and the 'agitation' to which the tuberculous ulcers are subjected) by reducing the diseased lung to a state of collapse. This would evidently be done by admitting the air into the cavity of the chest by an opening through the side, and preserving the passage to it free for a sufficient time. The lung would, by these means, be reduced to a state of quiet collapse, and the elastic fibers separated by the wound would be brought together. The lips of the divided surface would be brought into contact and the disease, if in one lung only, as frequently happens, would be cured by this process alone."[19]

He also knew that his suggestion had real possibilities in the treatment of pulmonary haemorrhage. He states that "a hemorrhage from one of the lungs, the frequent prelude to consumption, if not immediately fatal, would be as certainly stopped by the collapse of that lung, as the flooding consequent upon parturition by the contraction or rather the resilience of the womb" (6).

Carson endeavored to put his convictions to the acid test. Two far advanced, apparently hopeless cases afforded him the opportunity to try his method. An endeavor to collapse the lung was made by incising into the pleural space. Unfortunately, as postmortem examination revealed, the cases selected were unsuitable and the diseased lungs were firmly adherent and could not be collapsed.

Despite these two failures, he maintained "it has long been my opinion that if ever this disease is to be cured, and it is an event of which I am by no means disposed in all cases to despair, it must be accomplished by mechanical means, or in other words, by a surgical operation. Whether the method proposed will be found practicable, or, if practicable to the desired extent beneficial, or whether, as will be supposed by far most probable, it may amuse for a moment and then, like all its predecessors, sink into deserved neglect, are questions which must be left to the decision of time. Whatever may be the event, I shall have this consolation, that I incur no risk in this case by any proposition that may be made, of diverting the current of inquiry into a channel that shall be less productive than any of those in which it has hitherto run."[20]

[18] Page 51 of Carson's *An Inquiry into the Causes of Respiration.*

[19] Page 52 of Carson's *Respiration.*

[20] Page 63 of Carson's *Respiration.*

Carson's paper produced a momentary flutter of excitement and then fell into oblivion. Sporadic mention is made of Carson by later writers, but his classical efforts were regarded as fantastic, not feasible and unworthy of serious consideration.[21]

McRuer (36), in 1835,[22] after studies in the dissecting room, and from occasional references made in the literature, states, "The lungs are a double organ, each being capable of performing its function independently of the other;" and then asks, with reference to pulmonary tuberculosis, "Will we not be justified to suspend the action of a diseased lung by puncturing the chest?"[23] He presented a dubious case to support his claim but did not practice the method and the suggestion was ignored and soon forgotten.

Despite the work of these pioneers, the profession was not quite ready for collapse therapy in the treatment of pulmonary tuberculosis. Still another step had to be taken. It had to be clearly demonstrated that collapse of the lung by the presence of air in the pleural sac exerts a beneficial effect on the underlying tuberculosis. Credit for this advance goes to a host of clinicians who, during the last century, recognized that the appearance of a spontaneous pneumothorax may exert a favorable effect on the underlying pulmonary lesions and actually proposed in several instances the induction of artificial pneumothorax as a therapeutic procedure.[24]

Houghton appears to be the first to note clinical improvement following spontaneous pneumothorax. In 1832, he published an "account of a remarkable case of pneumothorax" in which the patient showed marked improvement. The patient, however, died at a later date, and at autopsy the author was able to demonstrate "an attempt at cure."[25] Five years later, Stokes presented cases in which improvement was shown following spontaneous pneumothorax. He states that "of the temporary suspension of the symptoms of phthisis there are now many

[21] Constatt, *Pathology and Therapy*, 1843; Wunderlich, *Pathology and Therapy*, 1856; Richter, *Principle of Internal Medicine*, 1856; Kohler, *Special Therapy*, 1867; Walsche, *Diseases of the Lung*, 1873.

[22] Waring (6) states that McRuer's article was brought to light by Lawrason Brown in May, 1932, at a meeting of the American Climatological and Clinical Association.

[23] Page 16 of McRuer, Boston, M. & S. J., 1835.

[24] Though many clinicians in the 19th century observed the beneficial effect that occasionally follows a spontaneous pneumothorax, many denied it. Bouffore, for example, as late as 1887, stated that phthisis is not arrested by spontaneous pneumothorax and that any improvement noted could be explained by the general condition of the patient.

[25] Houghton, Dublin, Journal of the Medical Sciences, 1832, page 313. Quoted by Emerson (27).

examples" and if the contralateral lung is not involved, the pneumothorax "really produces a temporary cure of consumption." He further adds "we know that the entrance of air by the cannula during paracentesis is a matter of trival moment."[26]

A host of observers (27, 37) followed at later dates with numerous case reports of phthisis favorably influenced by spontaneous pneumothorax.[27]

Biermer (27), in 1860, stated emphatically that it is well recognized that air, *per se*, in the pleural cavity, is not dangerous and that it is not a severe inflammatory agent. Desplats (38), in 1878, presented a number of cases which proved that pyopneumothorax is not a necessary complication of a spontaneous pneumothorax as many clinicians then believed. He insisted, from practical experience, on the harmlessness of aspirating the contents of the pleural cavity and cited cases so treated in which the effusion remained serous after paracentesis.

On clinical grounds Toussaint (2) set forth the claim for pulmonary collapse by pneumothorax. He presented, in 1881, numerous cases of phthisis which recovered following the advent of spontaneous pneumothorax or hydropneumothorax. In the same year, Herard and Mensuier (27) recorded similar observations.

Weil (37), in a work published the following year, discusses spontaneous pneumothorax and the effect that it has on phthisis. He presented several cases in which a beneficial effect was noted on the underlying tuberculosis—cases in which this condition either remained stationary or progressed at a slower rate than formerly. The author, however, felt that cases which underwent absolute cure were very rare. Knowing how simple it is to induce pneumothorax in animals (see above), Weil suggested the possibility of treating pulmonary phthisis by artificial pneumothorax.

At a meeting of the Royal Medical and Chirurgical Society in London, R. W. Parker presented a paper on *Suggestions for the Treatment of Special Cases of Empyema by Thoracentesis and the Simultaneous Injection of Purified Air* (39). The method was especially proposed for those cases of pleural effusion which could not be satisfactorily removed by aspiration. Bouchet, in France, had previously encountered the same difficulty and endeavored to solve it by forcibly expanding the

[26] Stokes, Dublin, Journal of the Medical Sciences, 1833, page 200. Quoted by Emerson.

[27] Among these may be mentioned Bach, Vaillez, Hughes, Banks, Newmann, Richter, Wintrich, Pollack, Traube and Czernicki.

lung by pumping air through a tube introduced into the bronchus. Parker believed this method far too drastic and in order to avoid, if possible, open drainage of the pleural contents, he advocated and practiced the injection of filtered and carbolized air while aspirating the pleural fluid.

Parker's suggestion was quite favorably received and in the ensuing discussion F. Hicks referred to three cases on which he had employed this method with favorable results. He proposed a modification of Parker's instrument, suggesting the attachment of a manometer to the side tube of the cannula, which enabled one to read the intrapleural pressures. He then presented an instrument of his own (a modification of Parker's) which made possible the irrigation of the pleural cavity with antiseptics as well as the injection of air.

Parker deserves recognition as being the first to systematically introduce sterile air into the pleural cavity as a therapeutic procedure.

Potain (40), in 1888, published his method of treating hydropneumothorax which he had been practicing for four years.[28] He practiced the aspiration of the pleural exudate and its substitution with sterile air or nitrogen. The maintenance of the pneumothorax, he argued, would keep the lung at rest and thus favor cicatrization and promote healing of tuberculous lesions. He presented two cases which had been rendered bacilli-free and cured by this therapy.

Ayerza (22), in Argentina, similarly practiced the injection of filtered air into the pleural sac. He used this method to facilitate the evacuation of exudates.

In 1885, Cayley (41) followed the suggestion made by Carson fifty years earlier and treated a severe case of pulmonary haemorrhage by incising into the pleural space and inserting a thoracotomy tube, thus establishing an open pneumothorax. He presented this case at a meeting of the Clinical Society of London. In the ensuing discussion, his attempt was referred to as a "heroic remedy." Parker thought the procedure rational but, in order to avoid risks of sepsis, he advocated the establishment of closed rather than open pneumothorax. He recommended the same procedure as he had been practicing in the treatment of certain types of empyemata. He favored the injection of filtered and carbolized air as previously described. It was further brought out at this meeting that a Doctor Mahomed[29] had previously recommended the

[28] Potain is often given credit for this method and the work of Parker is ignored, but clearly Parker deserves priority.

[29] We are unfortunately unable to find any publications by these two men.

induction of artificial pneumothorax to arrest phthisis and that a Dr. D. Powell[29] actually had practiced artificial pneumothorax therapy for cavernous pulmonary tuberculosis.

Adams (42), in 1887, having noted the beneficial effect on a case of cavernous pulmonary tuberculosis complicated by haemoptysis, advocated the establishment of an artificial pneumothorax by paracentesis of the chest for pulmonary tuberculosis and especially for uncontrollable haemorrhage. He felt that this procedure ought to be free from danger.

Späth (43), similarly impressed with the clinical demonstration of the beneficial effects that might follow spontaneous pneumothorax, mentioned artificial pneumothorax as a therapeutic possibility.

To these pioneers recognition must be extended for having laid the ground-work for the advent of artificial pneumothorax therapy. Their efforts established the fact that *paracentesis thoracis* is free from danger; that the introduction of air into the pleural cavity leads to collapse of the lung; that the air so introduced is harmless and not an inflammatory agent and that it may exert a beneficial influence. Further, in several instances, they proposed and actually practiced artificial pneumothorax therapy. These workers set the scene for the appearance of Forlanini and Murphy who deserve credit for withdrawing this procedure from the realm of speculation and placing it on a practical and scientific basis.[30]

Phthisiologists soon accepted this therapeutic advance and the practice of collapse therapy by artificially induced pneumothorax spread rapidly, leading to a greater knowledge of the possibilities and limitations of the method and to the invention of various types of apparatus.

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[30] The advocates of the new procedure met with considerable opposition at first. West, in 1897, attempted to refute the belief that pneumothorax has a therapeutic value and insisted that the healing of pulmonary phthisis is not favored by collapse of the lung. Bernard, in the same year, considered artificial pneumothorax dangerous but conceded that it might be used in a few selected cases. Gradually, however, new followers were won over and theoretical objections were overcome.

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TUBERCULIN SURVEY OF SCHOOL CHILDREN[1]

A Method of Case-Finding of Adult-Type Pulmonary Tuberculosis

E. S. JAMES

Three years ago Boyd (1) conducted a tuberculin survey of the primary grade school children in Vancouver for the purpose of determining the positive reactors and tracing if possible the source of their infection. Primary grade children were chosen because it was considered more likely that positive reactors among them would have received their infection within the home than would the older age groups.

A similar survey was carried out from November, 1937 to February, 1938 inclusive. Of a total receiving class of 3,247, permission to perform the test was granted in 1,742 cases, or 53.7 per cent. Of these, 83 were absent so that 1,659, or 51.1 per cent, of the children were actually tested. The tuberculin used was the same as in the previous survey (1). The technique employed in performing and reading the Mantoux test was identical with the previous survey with the exception that a dilution of 1:10,000 instead of 1:1,000 was used for the first dose.

As will be seen in table 1, 13.3 per cent of the children tested were positive reactors. This is a fairly substantial reduction from 20.1 per cent in the previous survey.

The sex incidence of tuberculous infection was not considered in this survey. Some investigators (2, 3, 4) have reported a higher incidence of reactors among females of this age group, while others (5, 6) reported a high incidence among males. In Boyd's (1) survey, the sex incidence was about equal.

Table 2 shows the variations in percentage of positive reactors according to race. The oriental group consisted of Japanese, Chinese and East Indians. In the previous survey these races were considered separately, but, since about 90 per cent of the orientals in the present survey were Japanese and the Chinese and East Indian groups were too small to be statistically significant, all were placed in one large group. Both white

[1] From the Tuberculosis Division of the Provincial Board of Health, under the direction of Dr. W. H. Hatfield, Vancouver, British Columbia.

and oriental groups showed a decrease in the percentage of positive reactors.

Of the 221 children who had positive reactions, 204 presented themselves for physical and roentgen examination (table 3). There was a

TABLE 1

Result of group tuberculin testing in two surveys, according to dosage

YEAR	1ST DILUTION			2ND DILUTION			TOTAL		
	Tested	Positive	Per cent	Tested	Positive	Per cent	Tested	Positive	Per cent
1934	1,001	52	5.2	917	149	16.2	1,001	201	20.1
1937	1,528	63	4.1	1,611	158	9.9	1,659	221	13.3

TABLE 2

Result of group tuberculin testing in two surveys, according to race

YEAR	WHITE			ORIENTAL			TOTAL		
	Tested	Positive	Per cent	Tested	Positive	Per cent	Tested	Positive	Per cent
1934	857	164	19.1	134	37	25.9	1,001	201	20.1
1937	1,465	182	12.4	194	39	20.1	1,659	221	13.3

TABLE 3

X-ray findings in two surveys, according to race

YEAR	RACE	NUMBER TESTED	NEGATIVE	POSITIVE	CALCIFIED LYMPH NODE AND PULMONARY NODULE	ACTIVE TRACHEO-BRONCHIAL LYMPHADENITIS	PARENCHYMAL INFILTRATION	PER CENT POSITIVE
1934	White	155	139	16	8	6	2	10.3
	Oriental	34	25	9	3	3	3	26.5
	Total	189	164	25	11	9	5	13.2
1937	White	169	137	12	10	2	0	7.1
	Oriental	35	29	6	3	1	2	17.1
	Total	204	166	18	13	3	2	8.8

considerable reduction in the percentage of demonstrable intrathoracic lesions in both racial groups, and in the recent survey most of the lesions were of the old calcified type.

Table 4 shows that the incidence of demonstrable intrathoracic lesions tended to increase with the size of the tuberculin reaction. A four-plus

reaction, however, did not necessarily indicate the presence of a demonstrable lesion, nor a one-plus reaction preclude a recent parenchymal infiltration.

TABLE 4

X-ray findings according to the size of the tuberculin reaction

YEAR	SIZE OF REACTION	NUMBER X-RAYED	NEGATIVE	POSITIVE	CALCIFIED LYMPH NODE AND PULMONARY NODULE	ACTIVE TRACHEOBRONCHIAL LYMPHADENITIS	PARENCHYMAL INFILTRATION	PER CENT POSITIVE
1934	+	110	105	5	2	2	1	4.5
	++	35	29	6	2	3	0	17.1
	+++	43	30	13	6	3	4	31.8
	++++	1	0	1	1	0	0	100.0
	Total	189	164	25	11	8	5	13.2
1937	+	109	103	6	4	1	1	5.5
	++	56	51	5	4	0	1	8.9
	+++	30	26	4	3	1	0	13.3
	++++	9	6	3	2	1	0	33.0
	Total	204	186	18	13	3	2	8.8

TABLE 5

Two surveys showing the influence of density of population on the incidence of tuberculous infection and X-ray findings

YEAR		NUMBER EXAMINED	NUMBER POSITIVE TO TUBERCULIN	PER CENT POSITIVE	NUMBER POSITIVE X-RAYS	PER CENT POSITIVE X-RAYS
1934	Area of most dense population	186	43	23.1	11	5.9
	Total area	1,001	201	20.1	25	2.5
1937	Area of most dense population	327	61	18.4	7	2.1
	Total area	1,659	221	13.3	18	1.1

In both surveys six schools situated in the area of densest population were grouped together (table 5). There was a higher percentage of positive reactors and demonstrable intrathoracic lesions in these schools, where the economic status was poor, than in the city as a whole.

In comparing the incidence of tuberculous infection and intrathoracic lesions in the white and oriental races, one must take into consideration

the poor economic status and crowded living conditions of most orientals in Vancouver. In order to make a more accurate comparison between the races, the children in the above mentioned six schools were selected. The economic status of these children were very similar. The percentage of reactors in the two races more nearly approximated one another in this district than in the general population (table 6).

A few years ago Slater and Jordan (7) suggested making a study of the home contacts of children who reacted to tuberculin for the purpose of discovering the source of infection. The possible sources are either the child's own family or casual contacts outside the home. Infection with the bovine bacillus was considered negligible since Vancouver's milk supply is largely pasteurized and the remainder is grade A milk from periodically tested cows.

It might be expected that school children of the primary grade age would have their intimate contacts more or less limited to their own

TABLE 6

Incidence of tuberculous infection and positive X-ray findings in whites and orientals of similar economic status

RACE	NUMBER EXAMINED	NUMBER POSITIVE TO TUBERCULIN	PER CENT POSITIVE	NUMBER POSITIVE X-RAY	PER CENT POSITIVE
White	167	28	17.0	2	1.2
Oriental	160	33	20.6	5	3.1

households, and therefore that examination of other members of the family of those children reacting to tuberculin would reveal the source of infection in a relatively large proportion of cases. Larsen and Halberg (8) in Denmark investigated the sources of infection among school children and were able to trace the primary source in 25 per cent of the cases. Boyd was able to trace the primary source in 29 per cent of cases.

In the present survey home contacts of the primary grade children were examined in the clinic. Positive reactors under thirty were given physical and roentgen examination. Contacts thirty years and over were considered tuberculin sensitive and the tuberculin test was omitted. Eighty-eight families have been examined to date, 56 completely and 32 incompletely. A family was considered complete when all the adults were examined. Of these families, 70 were white and 18 were orientals. Exclusive of the primary grade children there were 115 children examined, 71 whites and 44 orientals. There were also 133 adults ex-

amined. Of these, 109 were whites and 24 were orientals. The apparent source of primary infection was found in 10 cases, or 7.5 per cent. Four of these were already known to the clinic, the remaining 6 being new cases. It is interesting that 3 of the 6 new cases discovered were parents in families in which other children both older and younger than the primary grade child were not tuberculin sensitive. This would lead one to believe that these children may not have received their infection within the family after all. Of the 4 cases previously diagnosed 3 have died of far advanced disease and one was a minimal arrested case. The 6 new cases were all classified as minimal arrested. In addition 3 families gave histories of intimate contact with tuberculous individuals but this was not verified. The 6 adults with arrested pulmonary tuberculosis were found among 133 members of 88 families, an incidence of 4.5 per cent. In the previous survey the incidence of tuberculosis was 6.3 per cent among the adult group, but three-quarters of these were active cases.

The child contacts in the homes of the primary grade children ranged in age from birth to nineteen years inclusive. The average age in the first survey was 8.3 years, and in the recent survey 8.6 years. In the first survey the group numbered 133 and in the recent survey 115. Of these, 66.9 and 29.6 per cent respectively were positive reactors, while 13.6 and 5.2 per cent respectively showed demonstrable intrathoracic lesions. Although the percentage of reactors and demonstrable lesions showed a fairly marked reduction in the three-year interval, it was felt that these groups were too small to be statistically significant and were therefore not tabulated.

DISCUSSION

It is seen from the foregoing figures that the incidence of tuberculous infection among school children in Vancouver has materially diminished in the last three years. This was brought out in the decline in the incidence of tuberculin sensitive children, and the percentage of active intrathoracic lesions. The adults also showed definite falling off in the incidence of active pulmonary tuberculosis. The recent survey also showed that it is probable that 95 per cent of the primary grade children recieved their infections from casual contacts outside their homes.

During this interval there has been an active program for controlling the spread of tuberculosis in the Province, and a steady growth in the facilities for carrying out this program. All contacts or persons with suspicious symptoms may be examined and X-rayed in any of the station-

ary or travelling clinics. Children up to fifteen years of age are given routine Mantoux tests. Reëxaminations are done at frequent intervals on contacts and arrested cases, and active cases are segregated. All clinics in the Province are controlled by a central office so that individuals moving from one place to another can be kept under constant observation. In addition, occupational groups such as miners, telephone operators, school teachers, etc. are being investigated constantly.

With this falling off in the incidence of tuberculous infection in the community one would naturally expect any single survey for the purpose of case-finding to yield increasingly lower results as time went on. Three years ago the survey discovered 8 new cases; 6 of these were classified as "minimal, active" and would probably have been undiscovered for some time. When, however, the amount of tuberculous infection has decreased to a point where such a survey yields no active cases, the time has come to concentrate on the examination of groups which yield a higher percentage of active cases, such as contacts and individuals with suspicious symptoms.

SUMMARY

A method is described for attempting to discover cases of pulmonary tuberculosis by examining the contacts of tuberculin sensitive primary grade school children.

The incidence of positive tuberculin reactors among 1,659 primary grade school children was 13.3 per cent. The incidence among white children was 12.4 per cent and among orientals 19.1 per cent.

Demonstrable tuberculous lesions were found in 8.8 per cent of the positive reactors, 7.1 per cent in the white group and 17.1 per cent among the orientals.

The incidence of tuberculous lesions increased with the size of the tuberculin reaction, but the size of the reaction did not indicate the X-ray findings for the individual case.

The incidence of tuberculous infection and demonstrable intrathoracic lesions was somewhat greater among oriental than among white children of similar economic status.

Six new cases of pulmonary tuberculosis, all of which were classified as "arrested," were discovered among 133 adults.

The incidence of tuberculous infection and demonstrable intrathoracic lesions among the children of this survey has shown a considerable decline from the incidence of a previous survey.

Tuberculin testing of primary grade school children as a method of case-finding of adult pulmonary tuberculosis proved to be of little value in this survey.

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GROWTH AND METABOLISM OF TUBERCLE BACILLI[1,2]

The Rôle of the Source and Proportion of the Nitrogen in the Medium

ROBERT R. HENLEY AND PERCY W. LEDUC

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INTRODUCTION

The changes in reaction occurring in cultures of *Mycobacterium tuberculosis* grown on artificial culture media, proposed orginally by Smith (9) as a basis for distinguishing between the human and bovine types, have become, as pointed out by Wells and Long (12), of primary interest because of the light they throw upon the metabolism of the organism. Cobbett (1) basing his opinion upon a critical study of conflicting reports, chiefly those of Smith (9), Griffith (4) and Grund (5), concluded that the rate as well as the amount of growth determined the reaction of the culture filtrate. Henley (6) reported that the reaction at eight weeks appeared to be dependent upon the amount of growth made during the first three weeks regardless of the final weight of bacteria produced, of the type of organism and of the composition of the medium used. He thus apparently correlated the final reaction with the rate of growth. Weinzirl and Knapton (10) and Johnson and Renfrew (8) reported similar findings.

Henley and LeDuc (7) later reported that the final reaction of cultures

[1] From the Biochemic Division, Bureau of Animal Industry, United States Department of Agriculture, Washington, D. C.

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grown on media in which asparagine constituted the sole source of nitrogen was dependent on the relative amounts of asparagine and glycerol present; when the amount of nitrogen was relatively large the cultures remained alkaline and a lower proportion favored a change to an acid reaction. They also reported that cultures on an ammonium malate medium became acid, whereas cultures on an asparagine medium at the same nitrogen level had alkaline final reactions. Goyal (3) also reported that the final reaction of cultures on asparagine media depends upon the relative amounts of glycerol and nitrogen present. Wedum (11) found that the glycerol in his cultures was almost completely oxidized to carbon dioxide and water. He therefore suggested that any organic acid formed was immediately oxidized and that the decrease in pH value was not due thereto. He concluded that his results support the view that the acid produced by tubercle bacilli probably arises from the withdrawal of alkali from the medium.

During recent work in the laboratories of the Biochemic Division it has been found that glycine and the ammonium salts of glutamic and malonic acids can serve almost, if not equally, as well as asparagine and ammonium malate as sources of nitrogen for the growth of tubercle bacilli. It seemed likely that additional information regarding the influence of the source of nitrogen and of the relative amounts of glycerol and nitrogen upon the growth and metabolism of the organism could be obtained by studying the changes brought about by the growth of the bacilli on culture media of varying composition.

Accordingly a study was made of (*1*) the relation between the final reaction of the culture and the composition of the medium, (*2*) progressive changes in composition of the medium accompanying growth, (*3*) the maximum growths from media containing the five mentioned sources of nitrogen, (*4*) the relative potencies of tuberculins derived from cultures of different age and weight and from different culture media. The PN strain of the human type of the organism was employed.

EXPERIMENTAL

The relation between the final reaction of the culture and the composition of the medium: Differences in the composition of the media used in this work were obtained by preparing media from different sources of nitrogen and at different nitrogen and glycerol levels for each source. The sources of nitrogen were asparagine, glycine and the ammonium salts of glutamic, malic and malonic acids. Each type was prepared at three or

more different nitrogen levels between 0.08 and 0.32 per cent, and at each nitrogen level of each type at least two media were used which, although containing the same amount of nitrogen, contained different amounts of glycerol. The amounts of glycerol used were between 4 and 10 per cent.

The ammonium compounds were prepared by neutralizing the calculated amount of acid with ammonium hydroxide with litmus as an indicator. Except in very few instances, the correctness of the calculations was checked by subsequent nitrogen determinations.

In addition to glycerol and a nitrogen compound, each medium in all work reported in this paper contained per litre:

Dipotassium phosphate ($K_2HPO_4 \cdot 3H_2O$)	1.80 grams
Sodium citrate ($2Na_3C_6H_5O_7 \cdot 11\ H_2O$)	.90 gram
Magnesium sulphate ($MgSO_4 \cdot 7\ H_2O$)	1.50 grams
Ferric citrate, scales, U. S. P. VIII	.30 gram
Dextrose, U. S. P. X	10.00 grams

In all experiments 100 cc. portions of the medium were distributed in 300 cc. Erlenmeyer flasks and were sterilized under 15 pounds steam pressure for fifteen minutes. The total time of heating, that is, the time between turning steam on and removing the medium from the autoclave, was never permitted to exceed twenty-three minutes. The sterilized media were seeded from young cultures of the PN strain and were incubated at 37.5°C. At approximately weekly intervals two or more flasks of each culture were removed from the incubator and were sterilized by heating for three hours in flowing steam. The contents were then filtered through dried and tared papers, the bacteria were washed, dried at 100°C. and their weight was ascertained. The pH values of the filtrates were determined electrometrically by means of a glass electrode.

The week-by-week changes in growth and reaction were followed in order to ascertain whether in any of the different types of media there was a relation between the rate of growth and the final reaction, and also to decide which pH value should be considered the final one. The weekly changes will not be discussed in this section, but will be considered in detail later. However, it may be mentioned that the cultures increased in weight until a maximum was reached, and that the maximum was dependent on, but not proportional to, the amount of nutrients present and was independent of the source of nitrogen. The pH value began to change soon after the media were inoculated and continued to

change, provided the pellicles remained afloat, for weeks thereafter. Gross changes had usually ceased by the end of the ninth week and the reaction at that time is considered to be the final reaction.

In previous work (6) the final reaction appeared to be related to the rate of growth; the faster growing cultures were always the first to become acid. But the cultures were then grown on media which always contained the same amounts of glycerol and nitrogen. In the present work the cultures were grown on media containing different proportions of these nutrients and no relation appeared between the rate of growth and acid production. On the contrary, the faster growing cultures frequently had higher final pH values. However, a quite definite relation was found, as shown in table 1, between the glycerol:nitrogen ratio of the medium and the final reaction of the culture.

Included in the table are all cultures used in the work except a few which made little or no growth. At least four and in some instances

TABLE 1

The relation of the glycerol:nitrogen ratio of the medium to the final reaction of the culture

RATIO G:N	FINAL pH VALUES WITH DIFFERENT MEDIA				
	Asparagine	Glutamate	Glycine	Malate	Malonate
Below 35	7.6–8.1	7.2–8.5	7.5–8.3	6.5–7.9	5.9–7.1
36–79	6.0–7.7	6.1–8.5	5.5–7.9	4.8–7.5	5.1–6.9
Above 80	5.3–6.1	5.0–5.5	5.3–5.6	4.8–6.5	5.1–6.3

as many as seventeen media of each type were used in each indicated group of glycerol:nitrogen ratios. At ratios above 80 only one malate culture and one malonate had pH values above 6.0. These high pH values were probably due to the cultures becoming water-logged while the pH value was still relatively high. Thirteen out of fifteen malate and seven out of eight malonate cultures on media with glycerol:nitrogen ratios above 50 had final pH values below 6.0.

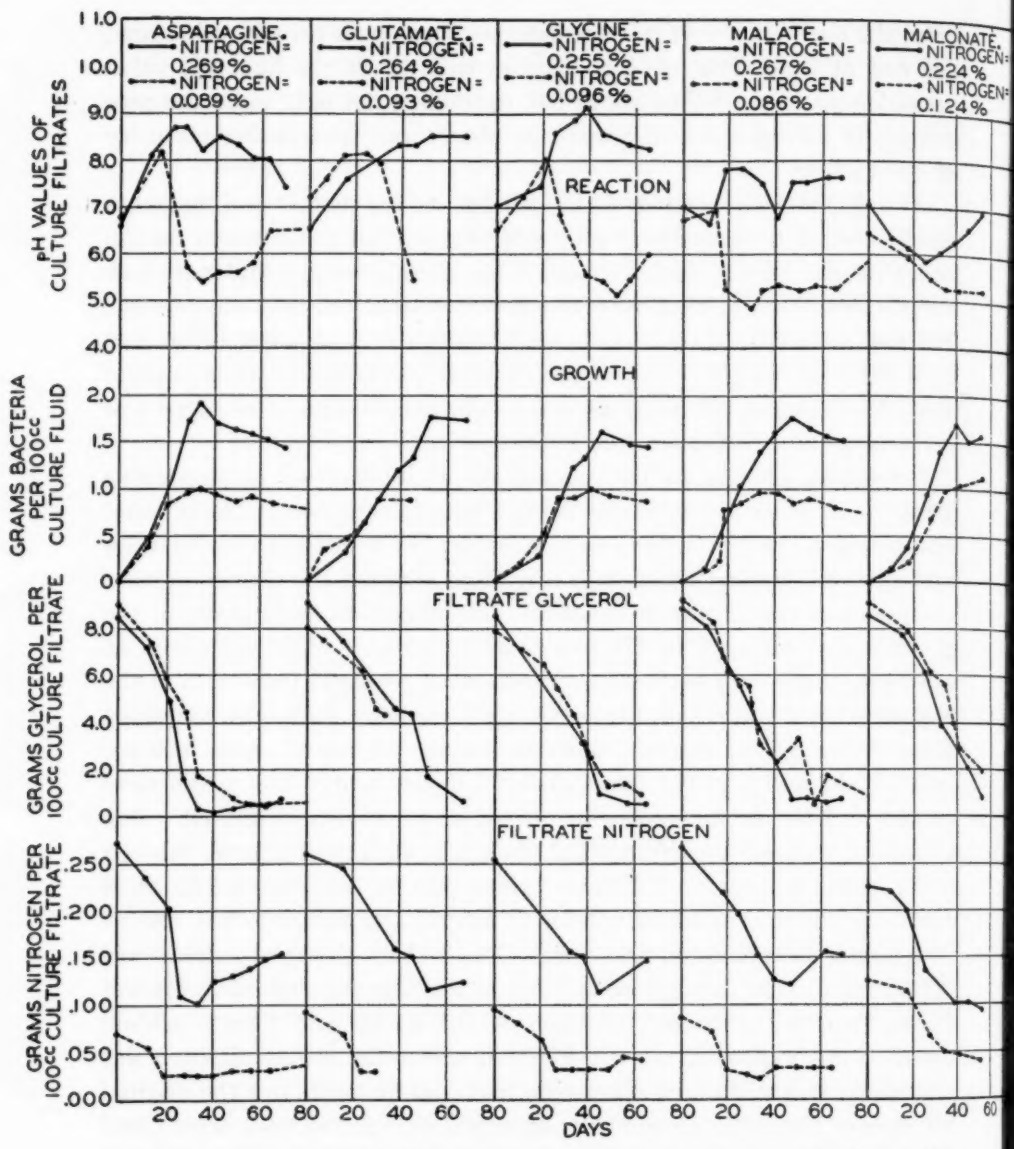
Regardless of the source of nitrogen, high final pH values were obtained at high nitrogen levels and low values at low levels. Thus when the glycerol:nitrogen ratio was 35 or less the final reaction of all cultures except those on malonate media was 7.0 or higher, but when the ratio was 80 or more the final reaction approached 5.0. Incidentally, on all media, except the malonate, with ratios of 35 or less the cultures became and remained alkaline from the beginning, whereas on media with very high ratios the cultures always became acid eventually and frequently

from the beginning. At intermediate nitrogen levels the pH value rose, fell and at times rose again so that at such levels the final pH value ranged from about 5.0 to above 8.0, depending not only upon the proportion of nitrogen but also upon its source and the relative maturity of the culture.

At any given nitrogen level the cultures on the malate and malonate media tended to have lower final pH values than the cultures on the other media, all of which contained an amino group. Malonate cultures seldom became alkaline even when abundant nitrogen was present, but malonate cultures on media with low glycerol:nitrogen ratios had final pH values higher than when the ratio was high. It thus appears that the source of nitrogen, as well as the proportions of nitrogen and glycerol present, influences the final reaction.

Progressive changes in the composition of the medium accompanying growth: In order to follow the changes which take place in the glycerol and nitrogen content of the medium during the growth of the organism and also to find whether there is a relation between the change in composition and the change in reaction, determinations were made of the glycerol and nitrogen in filtrates from cultures on different media at different stages of growth. Two media were prepared from each of the five mentioned sources of nitrogen. Both media of each type contained about 8 per cent of glycerol, but one of them contained about 0.09 per cent of nitrogen and the other about 0.26 per cent. The media were seeded and the cultures were incubated as previously described. One or more cultures were removed at intervals, sterilized, filtered through dried, tared papers, the filtrates were collected and the bacilli were washed until the combined volume of filtrate and washings was 150 cc. The bacteria were dried and weighed and their nitrogen content was determined. The nitrogen of the filtrate was also determined but it was found that the combined nitrogen of the bacilli and filtrate seldom equalled the original nitrogen. For that reason the filtrate nitrogen was calculated as the difference between bacterial nitrogen and the original nitrogen of the culture medium. Ammonia nitrogen was not determined in this series of experiments because a satisfactory procedure was not available.

The oxidizable organic matter of the filtrate was determined by the method used by Wedum (11) and is reported as glycerol. The composition of the media used, the intervals at which determinations were made and the results obtained are shown in graph 1.



GRAPH 1. Reaction, growth, filtrate glycerol and filtrate nitrogen curves of cultures of *M. tuberculosis* on media containing about 8 per cent glycerol and nitrogen in different amounts, about 0.08 and 0.32 per cent, from each of five different sources.

No relation was apparent between the amount of acid produced and the amount of glycerol consumed; the cultures in some cases became alkaline as glycerol disappeared. As much as 3 g. of glycerol were at

times consumed without causing any appreciable decrease in pH value. Three grams of glycerol oxidized to glyceric acid would require for neutralization 0.55 g. of ammonia which is more than was ever provided in any medium. This indicates that any acid produced by the oxidation of glycerol was shortly oxidized further to carbon dioxide.

Regardless of the weight of bacteria produced and regardless of the amount of nitrogen provided, practically all the glycerol in all of the media except the 0.093 per cent nitrogen glutamate medium disappeared and was undoubtedly consumed. With the exception noted, the organism continued to use glycerol after the culture had reached maximum weight and at times appeared to use glycerol while the weight was declining. In the glutamate medium noted, and in other cases not here described in detail, the culture reached full weight, limited by the amount of nitrogen supplied, but used only a portion of the glycerol. This never occurred with asparagine media but did occur with other types. In such cases the pellicles were often noticeably wet. The failure eventually to utilize all the glycerol present was probably due to the pellicles becoming water-logged. At any rate, when cultures were intentionally shaken down at any time during growth, glycerol no longer disappeared, whereas with all cultures which remained dry and continued to float, glycerol continued to disappear from the medium until only a negligible amount of oxidizable matter, probably not glycerol, remained. Since glycerol is not consumed after a culture is shaken down, its disappearance cannot be due to extracellular ferments. The disappearance of glycerol from cultures which are stationary or declining in weight indicates that glycerol is used chiefly for respiration. Incidentally the results afford a probable explanation of the observation which has been frequently made that on any medium fast growing cultures almost invariably reach a higher weight than more slowly growing ones—the slowly growing ones may exhaust, for respiratory purposes, the glycerol supply before the maximum possible bacterial weight is reached.

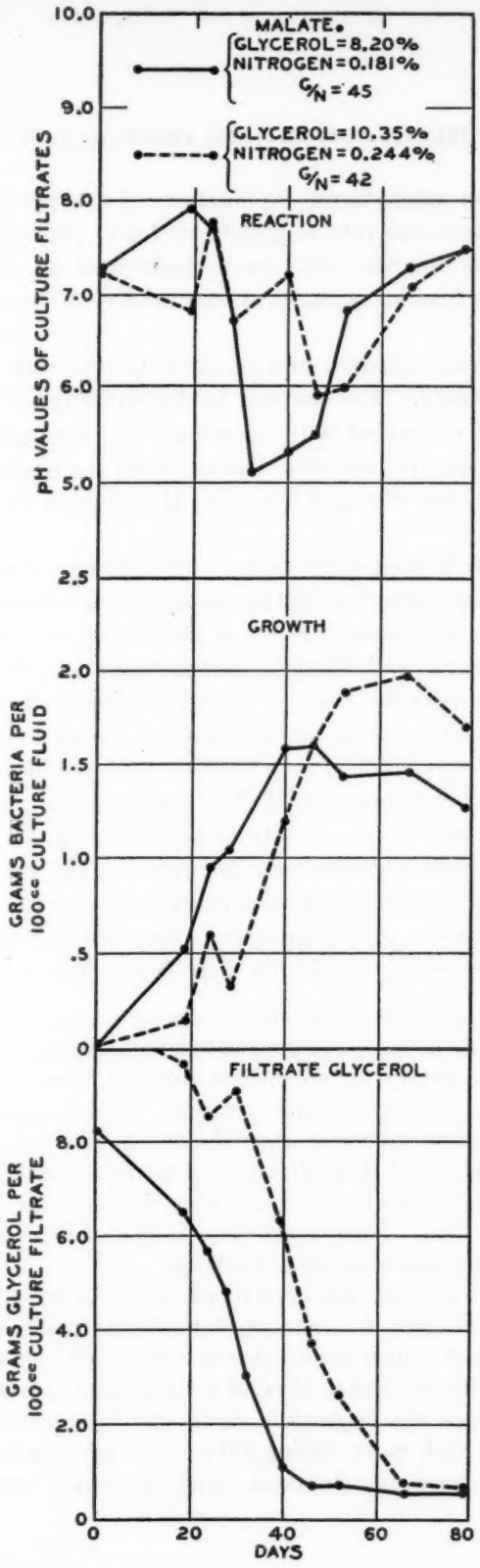
In the media of high nitrogen level the glycerol had largely disappeared about the time the cultures reached their maximum weights, and all these cultures, except the malonate, soon became and thereafter remained alkaline. The pH value of the malonate culture of high nitrogen content, 0.224 per cent, at first fell but rose after the glycerol had been reduced to a low level. In the media of low nitrogen level about one-half of the glycerol remained at the time maximum weight was reached or closely approached. About the same time, the pH value fell to 5.4 or

lower and there remained until the glycerol was reduced to a minimum after which there was a tendency, particularly in the cultures on the asparagine and glycine media, for the pH value to rise. The suggested connection between the depletion of the glycerol supply and the final rise in pH value was studied further in two experiments, carried out in the manner described above, with malate media containing intermediate amounts of nitrogen. Cultures on such media always exhibit a sharp rise in pH value after having previously become acid. The results are shown in graph 2.

The two media contained different amounts of glycerol and nitrogen and, as usual under such conditions, the cultures made different amounts of growth. However, the glycerol:nitrogen ratios of the two media were quite similar and the reaction curves were, as was expected, much alike. After first becoming alkaline both cultures became acid, the reaction of both falling below pH 6.0 by the time the glycerol had been reduced to about 2 g. per 100 cc. As the glycerol of the media became further depleted the reaction again rose, reaching about pH 7.5 in both cultures after the glycerol had been reduced below 1 g. per 100 cc., that is, the final rise in pH value occurred after the glycerol supply had been practically exhausted.

The tendency of cultures of acid-fast organisms to revert to neutrality, if not alkalinity, after having first become acid has been generally noted and different explanations have been advanced. The results here reported seem to indicate that the rise is connected with the disappearance of glycerol and there is a further suggestion that the rise is more pronounced when the residual nitrogen is above 0.05 g. per 100 cc. It seems possible that the organism may, after the glycerol has been exhausted, attempt to obtain energy by attacking the anion of salts of organic acids thus leaving an alkaline residue which may or may not be ammonia. If a great excess of glycerol is originally present it may not be so completely used, other organic compounds would not be attacked and the culture would remain acid. The suggested explanation applies only to the final and not to the initial rise in pH values; a possible explanation of the formation of alkali or acid in the earlier stages will be discussed later.

Although the figures given for nitrogen in the different experiments are of only partial significance because an undetermined part of the filtrate nitrogen is due to the products of bacterial growth, it may be noted that in practically all cases (graph 1) filtrate nitrogen was reduced to a minimum about the time maximum weight of bacteria was reached.



GRAPH 2. Reaction, growth and filtrate glycerol curves of cultures of *M. tuberculosis* on malate media containing different amounts of glycerol and nitrogen but at about the same glycerol:nitrogen ratio.

This observation suggests an explanation of the previously reported connection between the rate of growth and acid production; when two cultures grow at different rates on a single medium, the faster growing culture is the first to become acid because it is the first to exhaust the nitrogen supply.

After the filtrate nitrogen had reached its minimum a definite rise was sometimes noted. The rise may be due to bacterial leachings but it is probably not connected with occasional accompanying rises in pH values because when pellicles were shaken down the bacteria appeared to lose weight and also nitrogen but the pH values of the cultures were unaffected.

Because of the limited significance of the nitrogen results obtained in the foregoing experiments a further study of the nitrogen metabolism of the organism was made. For this purpose seven asparagine media of different glycerol and nitrogen content were prepared, seeded and incubated as previously described. Asparagine was selected as the source of nitrogen because it contains both an amino and an amid group. At intervals three cultures of each medium were sterilized, filtered separately through tared papers, and the bacteria from each flask were washed until the combined volume of filtrate and washings was 150 cc. The filtrates from similar cultures were combined. The weight of bacteria and their nitrogen content were determined as were the pH values and the glycerol contents of the filtrates. The amid-, amino-, ammonia- and protein-nitrogen of the filtrates were determined on 75 cc. aliquots.

The procedure used for determining ammonia nitrogen was based in part upon the method described by Cullen and Van Slyke (2) for removing ammonia from proteins precipitated by ammonium sulphate, namely, distillation with magnesium oxide from an alcoholic solution. Freshly prepared asparagine media yielded no free ammonia when distilled in this way, but ammonium malate media yielded all their nitrogen. Asparagine media yielded one-half, the amid nitrogen, of their total nitrogen when distilled with sodium hydroxide from a water solution. Based upon these findings a procedure was adopted which involved the following determinations:

Total bacterial nitrogen was determined in one or more lots of bacteria, and total filtrate nitrogen in an aliquot of the filtrate by digestion and distillation. Nitrogen per sodium hydroxide was determined by diluting an aliquot of the filtrate to 500 cc., adding 25 cc. of a 1:1 sodium hydroxide solution and distilling. Nitrogen per magnesium oxide was determined by diluting an aliquot to 300 cc. with water, adding 300 cc. of 95 per cent alcohol and 5 g. of magnesium oxide previously ground in a small amount of water and distilling.

Protein-nitrogen, that is, the nitrogen contained in the precipitate obtained by the addition of 25 cc. of a 40 per cent solution of trichloracetic acid to 75 cc. of the culture filtrate, was determined only in the older cultures. The amid-, amino-, and ammonia-nitrogen were obtained from these determinations by the following calculations:

1: Original nitrogen of the medium − bacterial nitrogen = total nonbacterial nitrogen
2: Total nonbacterial nitrogen − total filtrate nitrogen = nitrogen lost by volatilization during growth and sterilization
3: Lost nitrogen + nitrogen per magnesium oxide = ammonia nitrogen
4: Nitrogen per sodium hydroxide − nitrogen per magnesium oxide = amid nitrogen
5: Total filtrate nitrogen − nitrogen per sodium hydroxide = amino nitrogen

The changes brought about by the growth of the organism on the asparagine media are reported in table 2.

The close agreement between successive determinations of the same form of nitrogen in the same culture after it had reached full weight indicates that the results are reliable. The close agreement of the results of the analyses on the twenty-sixth day with those of the following days of culture 146A and also of culture 146B is illustrative. The only noticeably discrepant result is that for amino-nitrogen, culture 146C, on the thirty-third day. The small amounts of ammonia in the original media of cultures 146A, B and C were possibly due to the fact that these media were held for several weeks before they were examined. All other media were analyzed within a few days from the time that they were prepared.

The cultures grew unusally fast and the reactions on the fortieth day probably correspond to the final reactions of older but more slowly growing cultures. From the thirty-third day on, the previously noted relation between the glycerol:nitrogen ratios of the media and the final reactions held with these cultures as with those previously described.

Changes in the amounts of the different forms of nitrogen began soon after the media were seeded and continued until maximum growth was reached, thereafter changing but slightly. Thus a sharp drop in the amino- and amid-nitrogen and a marked rise in the ammonia-nitrogen took place within the first two weeks of incubation, and by the third week practically all the amid- and a considerable part of the amino-nitrogen of the asparagine had been converted to ammonia or utilized by the

TABLE 2

*Changes in the pH values, glycerol and forms of nitrogen brought about by the growth of M. tuberculosis on asparagine media of different glycerol:nitrogen ratios**

CULTURE NUMBER	MEDIUM			AGE OF CULTURE	BACTERIA		CULTURE FILTRATE						
	Asparagine added	Glycerol added	G : N ratio		Weight	Nitrogen	pH value	Glycerol found	Forms of nitrogen				
									Total	Amino	Amid	Ammonia	Protein
	gram	*grams*		*days*	*grams*	*gram*		*grams*	*gram*	*gram*	*gram*	*gram*	*gram*
145A	0.50	4.00	42	0	0.00	.000	6.8	5.02	.098	.050	.048	.000	
				12	0.56	.042	7.5	3.42	.056	.014	.007	.035	
				19	1.11	.074	6.5	1.34	.024	.018	.001	.005	
				26	1.03	.076	6.4	0.06	.022	.013	.003	.006	.006
				33	1.02	.074	6.4	0.20	.024	.016	.000	.008	.006
				40	0.99	.076	6.8	0.07	.022	.014	.003	.005	.006
				47	0.90	.072	6.6	0.07	.026				.006
145B	0.50	9.00	95	0	0.00	.000	6.8	9.30	.100	.051	.049	.000	
				12	0.27	.023	7.7	8.20	.077	.022	.015	.040	
				19	0.92	.069	6.1	6.32	.031	.017	.003	.011	
				26	1.04	.074	5.6	3.88	.026	.011	.005	.010	.005
				33	1.04	.072	5.6	3.36	.028	.016	.001	.011	.006
				40	1.06	.072	5.5	0.69	.028	.015	.003	.010	.004
				47	1.01	.070	5.1	0.81	.030				.004
146A	0.75	5.00	35	0	0.00	.000	7.0	5.86	.144	.074	.063	.007	
				12	0.45	.033	8.2	4.91	.111	.029	.017	.065	
				19	1.22	.099	8.7	2.50	.045	.012	.012	.021	
				26	1.52	.104	7.2	0.40	.040	.020	.006	.014	.008
				33	1.41	.109	7.0	0.39	.035	.022	.004	.009	.009
				40	1.39	.106	7.1	0.20	.038	.020	.003	.015	.008
				47	1.33	.107	7.0	0.20	.037				.007
146B	0.75	7.50	53	0	0.00	.000	6.9	8.10	.144	.074	.064	.006	
				12	0.31	.020	7.9	7.28	.124	.042	.037	.045	
				19	1.01	.076	7.9	5.27	.068	.029	.005	.034	
				26	1.47	.109	6.8	3.04	.035	.019	.005	.011	.008
				33	1.45	.109	6.1	0.47	.035	.022	.002	.011	.007
				40	1.35	.106	6.6	0.20	.038	.021	.001	.016	.006
				47	1.37	.103	6.5	0.26	.041				.008
146C	0.75	10.00	70	0	0.00	.000	6.9	10.50	.144	.072	.068	.004	
				12	0.29	.016	7.6	9.50	.128	.045	.040	.043	
				19	0.70	.050	8.7	8.54	.094	.024	.000	.070	
				26	1.23	.092	8.1	5.98	.052	.022	.004	.026	.008
				33	1.40	.118	5.9	3.15	.026	.011	.013	.002	.006
				40	1.41	.112	6.0	1.44	.032	.019	.004	.009	.005
				47	1.37	.104	5.5	0.81	.040				.006

TABLE 2—*Concluded*

CULTURE NUMBER	MEDIUM			AGE OF CULTURE	BACTERIA		CULTURE FILTRATE						
	Asparagine added	Glycerol added	G : N ratio		Weight	Nitrogen	pH value	Glycerol found	Forms of nitrogen				
									Total	Amino	Amid	Ammonia	Protein
	grams	*grams*		*days*	*grams*	*gram*		*grams*	*gram*	*gram*	*gram*	*gram*	*gram*
147A	0.40	8.00	107	0	0.00	.000	6.9	8.38	.075	.036	.039	.000	
				12	0.32	.017	7.5	7.63	.058		.013		
				19	0.81	.056	7.1	5.86	.019	.013	.003	.003	
				26	0.88	.056	5.8	3.75	.019	.010	.002	.007	.002
				33	0.87	.057	5.3	2.57	.018	.011	.001	.006	.002
				40	0.83	.054	5.5	1.50	.021	.011	.002	.008	.003
				47	0.78	.056	5.0	0.75	.019				.003
147B	1.20	8.00	35	0	0.00	.000	6.9	8.50	.208	.096	.112	.000	
				12	0.36	.026	7.8	7.41	.182		.057		
				19	1.02	.085	9.0	5.44	.123	.030	.002	.091	
				26	1.79	.151	8.0	2.20	.057	.032	.006	.019	.011
				33	1.88	.157	7.0	0.20	.051	.032	.005	.014	.011
				40	1.78	.151	7.4	0.00	.057	.034	.007	.016	.012
				47	1.72	.144	7.1	0.34	.064				.011

* Results stated in grams per 100 cc.

organism. It seems quite probable that the initial rise in pH value is to be attributed to the liberation of ammonia. It also seems quite likely that the residue left after the removal of ammonia is either neutral or is readily and immediately utilized. If the residue were acid, the pH value would not rise.

It is generally recognized that among the reactions occurring during the decomposition of amino and other organic acids by microörganisms are reactions involving deaminization and decarboxylation accompanied by the reduction of acids to alcohols of fewer carbon atoms. It seems possible that the tubercle bacillus may employ similar reactions to break down compounds such as asparagine and ammonium malate, in which case reactions such as the following may take place.

$$NH_2OC \cdot CH_2 \cdot CHNH_2 \cdot COOH + 2H_2O = 2NH_3 + 2CO_2 + CH_3 \cdot CH_2OH.$$
(asparagine)

$$NH_4OOC \cdot CH_2 \cdot CHOH \cdot COONH_4 = 2NH_3 + 2CO_2 + CH_3 \cdot CH_2OH.$$
(ammonium malate)

The reactions may not occur as indicated, but it is interesting that similar reactions occur with other microörganisms and that reactions of the type illustrated could account for the liberation of ammonia and the simultaneous formation of neutral residues. In this connection it has been found that distillates from growing cultures of tubercle bacilli yield positive iodoform tests, indicating the presence of alcohol, and that the organism is able to grow on media in which alcohol in small amounts, one per cent or less, is the sole organic compound present aside from traces of organic acids.

In all cultures which became acid the fall in pH value occurred about the time that the filtrate nitrogen and ammonia nitrogen were reduced to a minimum. No consistent relation was detected between the final pH value and residual ammonia. After the glycerol had been exhausted there was in these, as in other experiments, a tendency for the pH values to rise.

Protein nitrogen was determined only in the later weeks. The amounts found were small but indicate that a considerable part of the residual nitrogen of the filtrates of the more mature cultures is protein in character and it may well be that all the filtrate nitrogen found during the later weeks in all cultures except 147B represents nitrogenous substances elaborated by the bacteria rather than unused nitrogenous nutrients of the media. Culture 147B was grown on a medium containing a relative excess of nitrogen.

At and after the fortieth day of the two or more cultures in each experiment the filtrate with the highest pH value contained the highest amount of protein nitrogen. Although the numerical differences in the amounts of protein nitrogen found in filtrates of high and low final pH values were very small the visible differences in the amounts of precipitates produced by trichloracetic acid in such cultures were quite noticeable.

At the time of maximum growth the nitrogen content of the dried bacteria ranged from about 6.5 to 8.4 per cent. The percentages of nitrogen in the bacteria differed not only in bacteria grown on different media but also in bacteria of different ages from the same medium. No consistent relation was detected between the percentage of bacterial nitrogen and any constituent of the medium.

In addition to the sources of nitrogen previously mentioned, alanine, glycyl-glycine and the ammonium salts of aspartic and fumaric acids afforded reaction curves and growth curves similar to those of asparagine, that is, yields ranging from 1.50 to 2.0 g. bacteria per 100 cc. of culture

fluid were obtained and, when the proportion of nitrogen was high, cultures on these media remained alkaline throughout. On some other amino-acid media, such as aminobutyric and aminovaleric acids, and upon some ammonium compounds, such as the acetate, oxalate and sulphate, the organism was able to make only a limited amount of growth, but the pH value, regardless of the proportion of nitrogen present, fell from the beginning. Thus an oxalate medium afforded a growth of 0.14 g. and the reaction fell to pH 4.6; a sulphate medium afforded a yield of 0.25 g. and the pH fell to 4.0. With ammonium salts of weaker acids the reaction seldom fell below pH 5.0 and never below pH 4.7. The extent of fall thus appears to be related to the source of nitrogen. The results obtained with the different types of nitrogen compounds suggest that the compounds which fail to afford good growth leave, after the loss

TABLE 3

*The influence of the amount of buffer present on the amount of acid produced**

MEDIUM NUMBER	ASPARAGINE MEDIA			COMPOSITION OF CULTURE, 41ST DAY				
	Composition			Weight Bacteria	Filtrate			
	Nitrogen	Glycerol	Phosphate $K_2HPO_4 \cdot 3H_2O$		pH	Nitrogen	Glycerol	$\frac{N}{10}$ acid†
	gram	*grams*	*gram*	*gram*		*gram*	*grams*	*cc.*
1	.089	9.00	0.18	0.93	5.4	.025	1.35	5.6
2	.089	9.25	0.54	0.92	5.3	.023	1.65	21.3

* Results in grams, or cc. per 100 cc. of original medium.

† Phenolphthalein as an indicator.

of nitrogen, residues which are not utilized, but which accumulate and, being acids, finally reduce the pH value to a point at which growth is inhibited. On the other hand, those compounds upon which the organism grows well may have residues which are utilized and thus do not contribute to the production of acid.

Whether a culture becomes acid depends upon the source and proportion of nitrogen present in the medium, but the amount of acid produced is related to the amount of buffer present as indicated in table 3.

Here two cultures grew to the same weight, used the same amounts of glycerol and fell to the same pH, but produced distinctly different amounts of acid. If equal amounts of glycerol are oxidized, equal amounts of acid should be produced provided the end result of oxidation is an acid. Unless the acid is volatile it should accumulate. Certainly

there appears to be no relation between the amount of glycerol consumed and the amount of acid produced. A volatile acid, carbonic, is probably produced by the oxidation of glycerol but the acid responsible for the lowering of the pH value is nonvolatile. Passage of carbon dioxide into culture filtrates has depressed their pH values from above 7.0 to as low as 5.7, but when the filtrates were heated the pH rose above 7.0 again. All filtrates used in this work were heated for three hours in flowing steam. It seems likely that a relatively weak acid is produced as an intermediate product of glycerol metabolism and that, whereas the amount produced depends upon the amounts of bacteria and glycerol present, the amount remaining undecomposed depends on the amount of buffers present.

Maximum growth afforded by various media: During the course of this work the growth and reaction curves of more than one hundred cultures have been determined with consequent accumulation of considerable information regarding the yields from cultures grown on media containing different amounts of glycerol and nitrogen. In order to avoid confusion of detail, the results have been analyzed and are summarized below.

The yields, although dependent upon the amounts of glycerol and nitrogen in the media, were never proportional to the amount of glycerol nor, except possibly at low levels, to the amount of nitrogen present.

Except with ammonium malate, no attempt was made to find, for each nitrogen compound, the exact amount of glycerol and nitrogen which would afford the maximum yield of bacteria per 100 cc. of medium.

The highest yield obtained was 2.20 g. of bacteria from a malate medium containing 0.32 per cent nitrogen and 8.0 per cent glycerol. Yields of at least 2.0 g. were obtained from each of the other types of medium except glycine from which the highest weight found was 1.81 g. The highest actual yields were found when the yields per gram nitrogen and glycerol were low, and all media, except the malonate, which afforded high actual yields had final pH values above 6.9. With glycerol at 10.0 per cent and an abundant supply of nitrogen as evidenced by a decidedly alkaline final reaction, the glycerol has been entirely consumed with yields not exceeding 2.20 g. per 100 cc. of culture fluid. Slight further increases in the amount of glycerol have decreased the yield and still larger increases have inhibited growth. The optimum concentration of glycerol seems to be about 10.0 per cent and that of nitrogen about 0.32 per cent. Yields consistently exceeding 2.20 g. are not to be expected with the human type of organism.

Based upon the amount of nitrogen originally provided in the media, the maximum yield of bacteria per gram nitrogen was, with each type of medium, obtained from a medium of low nitrogen level, the final reaction was acid and the actual yield was small. The highest yield per gram nitrogen was 12.0 g. of bacteria afforded by a malate medium which contained 0.09 per cent of nitrogen. Yields of at least 10.0 g. of bacteria per gram nitrogen were obtained from each of the five sources of nitrogen. Some asparagine media afforded yields slightly in excess of 10.0 g. of bacteria per gram nitrogen and had final reactions above 7.0, whereas all other media affording equivalent yields had decidedly acid final reactions.

Based upon the amount of glycerol originally provided in the media, the maximum yield per gram glycerol was obtained, with each type of medium, from a medium of low glycerol level; the final reaction was, in all cases, above pH 6.85 and the actual yield was small. The highest yield per gram glycerol (0.38 g.) was afforded by an asparagine medium which contained 4.0 per cent glycerol, and six other asparagine media afforded yields of at least 0.30 g. per gram glycerol. The other media never afforded yields in excess of 0.29 g. bacteria per gram original glycerol.

The relatively small yield per gram glycerol and the relatively large yield per gram nitrogen again suggest that glycerol is used largely in respiration and nitrogen for reproduction.

Asparagine and malate media have always afforded yields such as were expected from the amount of nutrients present. In several instances the pellicles fell in malonate media before full expected weight was reached, but the media were reinoculated and then afforded the anticipated yields. Glycine media are very easily injured by overheating. When such media were prepared without dextrose and a sterilized solution of dextrose was added later to the sterilized glycine medium, as suggested by Wong (13) for malate medium, rapid and abundant growth was always obtained. Cultures on glutamate media had an unusually high ash content and quite frequently fell before full weight was reached. At low nitrogen levels they frequently failed to grow, and at high levels growth was not dependable. In some cases better growth was obtained on glutamate media when about one-third of the distilled water was replaced by tap water. This suggests that the salt mixture regularly used may fail to supply a sufficient amount of some mineral necessary for full growth on glutamate media.

Several attempts were made to ascertain the influence of the source of

nitrogen on the rate of growth. The work was carried out before all the factors influencing the rate of growth on the glycine and glutamate media were understood, and the results therefore are not entirely dependable. In all experiments the cultures on the asparagine media grew at the fastest rate, but the differences were not great. The conclusion, applying only to the five sources of nitrogen studied, was reached that the source of nitrogen is one of the less important factors influencing the rate of growth.

There was also very little difference in the rates of growth of cultures upon media containing different amounts of nitrogen from one source. However, it is possible that the proportion of nitrogen most favorable for rapid growth upon one type of medium may not be the most favorable with another type.

The experiments have shown that with any of the five sources of nitrogen mentioned it is possible to obtain a diversity of yields and final reactions by alterations in the proportions of glycerol and nitrogen. In this connection it may be mentioned that the yields and final reactions of cultures on malate media containing 0.32 per cent nitrogen and 8 per cent glycerol closely approximated those obtained with the asparagine medium (0.27 per cent nitrogen and 10 per cent glycerol) routinely used to produce tuberculin. It has also been found, as a point of possible interest, that the yield from the old type of beef-infusion medium can be increased from a previous average of less than 0.60 g. to about 1.50 g. per 100 cc. by adding 2.0 per cent of peptone, instead of 1.0 per cent, together with a small amount of ferric citrate.

The relative potencies of tuberculins derived from different media: From time to time cultures of known antecedents were filtered and the bacteria were washed with water until the volume of the combined filtrates and washings from each flask was 180 cc., to which 20 cc. of a 5 per cent solution of phenol were added as a preservative. Later the preserved filtrates were diluted, and their relative potencies were ascertained by comparative intracutaneous tests on sensitized guinea pigs. The weight and pH values of the cultures were determined at the time of filtration but the dilutions used for test were based upon the highest weight observed at any time during growth and not upon the weight at the time of filtration. Two dilutions were prepared in one of which the dose (0.05 cc.) was derived from 0.005 mg. of bacteria and in the other from 0.001,7 mg. The injections were made by one worker, the readings were made by another and neither worker was acquainted with the history of the

TABLE 4

Relative potencies of tuberculins derived from different media

TEST	MEDIUM	WEIGHT BACILLI PER 100 CC. MEDIUM	pH VALUE	RESULTS OF SKIN TESTS			
				Tuberculin from .005 mg. bacteria		Tuberculin from .001,7 mg. bacteria	
				G.P.I.	G.P.II.	G.P.III.	G.P.IV.
1	Asparagine	1.21	7.5	¼	?		¼
	Beef broth	0.59	5.6	½	1	?	¼
	Glutamate	2.06	8.6	¼	¼		¼
	Glycine	0.77	5.3	¼	¼		?
	Malate	2.07	6.7	¼	¼	?	?
	Malonate	1.71	5.9	¼	?	?	¼
2	Asparagine	1.36	6.8	1	1¼	¼	1
	Beef broth	0.90	5.3	¾	¾	¼	1
	Glutamate	2.07	8.1	1	1¼	½	1
	Glycine	1.57	7.8	1¼	1	½	1
	Malate	1.74	4.8	1	1	½	1
	Malonate	1.62	6.9	1	1¼	¼	1
3	Asparagine	1.21	6.9	3	3	?	2
	Asparagine	1.26	6.5	3	3	?	2
	Malate	1.07	6.5	3	3	?	2
	Malate	1.00	4.9	3	3	¼	2
	Malonate	1.06	6.8	3	3	?	1
	Malonate	0.93	5.6	3	3		2
4	Asparagine	1.21	7.5	1	2	¼	¼
	Beef broth	1.55	6.7	3	4	3	1
	Glutamate	2.06	8.6	3	4	2	1
	Glycine	1.57	7.8	2	4	¼	1
5	Glycine	0.77	5.3	1	½	2	½
	Glycine	1.57	7.8	2	1	3	½
	Malonate	0.90	5.2	1	½	2	½
	Malonate	1.71	5.9	2	1	3	1
6	Glutamate	2.04	6.9	4	3	1	½
	Malonate	1.46	5.9	4	1	¾	¼
	Malate	1.85	7.4	3	1	¾	¼
	Malate	0.85	5.0	4	1½	¾	¼
7	Malate	0.94	4.8	4–2*	½–2*	¼–¼*	½–1*
	Malate	1.73	7.7	2–1	2–2	1–1	1½–1½
	Malate	1.87	8.0	1–2	2–2	1–1	1½–1½
	Glutamate	2.06	8.6	4–3	2–2	1–1	½–1

* Two tests of the same tuberculin were made simultaneously on the same guinea pig.

products tested. The system used to mark the reactions was to select one definitely positive reaction in each test and to mark this as "1." Other reactions were graded according to their variation in size, thickness and appearance from the one selected as a standard. Results are shown in table 4.

When the same tuberculin was tested, as in test 7, in duplicate on the same guinea pig the results of the duplicate tests agreed in only 9 out of the 16 tests. When the different tuberculins were tested on the same guinea pig, the disagreement between the different tuberculins was no greater than the disagreement between duplicate tests of the same tuberculin. Although there is a lack of uniformity, and although it is possible that there were differences in the potencies of the different tuberculins which were not detected, the results, considered as a whole, show that potent tuberculins were obtained from cultures grown on six different sources of nitrogen, including beef-infusion medium. Further, when the tuberculins were tested on the basis of the weight of bacteria from which they were derived, no appreciable differences in the potencies of the different tuberculins were consistently found.

DISCUSSION

The explanation attributing alkali production by cultures of *M. tuberculosis* during their early stages of growth on artificial culture media to the formation of ammonia, is quite generally accepted and is supported by the observations made during this work.

Among the explanations of acid production which have been advanced, two have received the most general support. One attributes acid production to the selective absorption of the alkaline constituents of the medium, the other to oxidation products of glycerol. It is difficult to reconcile the first with the observation that upon sources of nitrogen which support abundant growth there is no relation between the amount of growth and acid production. Further, no relation was detected between the final reaction of a culture and the amount of residual ammonia in the filtrate.

The suggestion by Wedum (11) of the formation of an acid as an intermediate oxidation product of glycerol seems to meet his own objection to considering glycerol as the source of acid. He thought that the small amount of oxidizable matter remaining in his cultures precluded the possibility of an organic acid being responsible for the acid reaction. In the work here reported only 5.6 cc. of N/10 sodium hydroxide, equivalent

to 0.059 g. of glyceric acid, was required to neutralize 100 cc. of a culture filtrate of pH 5.4. The amount of oxidizable matter remaining in all acid cultures examined was much greater than 0.059 g. Further, although an acid produced as an oxidation product might be only a transition product, it would affect the pH value as long as it was present, it would be present as long as glycerol remained, its amount would depend on the amounts of glycerol, bacteria and buffers present, and its presence could be masked by the presence of ammonia, which in turn would be present as long as the nitrogen supply of the medium remained above the nitrogen requirements of the bacteria. In all respects, the results obtained in this work, particularly the observed relation between the glycerol:nitrogen ratio of the medium and the final reaction, point to glycerol as the chief source of acid, and it seems probable that the reaction changes are brought about in somewhat the following manner.

When inoculated on a suitable medium the organism begins to oxidize the glycerol and to decompose the nitrogenous compounds. The glycerol is probably oxidized through an intermediate acid to carbon dioxide and water, but since the number of organisms at first present is few the rate of oxidation is low. The results seem to indicate that nitrogen, unless present as ammonia, is converted to ammonia before it is utilized, and that different types of nitrogenous compounds are probably broken up by different mechanisms. Asparagine, glycine and ammonium glutamate are probably deaminized with the relatively rapid liberation of free ammonia and the formation of residues which are either neutral in reaction or else are immediately utilized and thus do not affect the pH value of the culture. At the other extreme are compounds such as ammonium sulphate from which ammonia seems to be absorbed directly, leaving non-utilizable acid residues which accumulate and prevent further growth. Ammonium malonate perhaps occupies an intermediate position—the organism absorbs ammonia directly and leaves an acid residue, but this is eventually utilized. Ammonium malate more closely resembles the asparagine group.

As growth progresses glycerol becomes oxidized more rapidly, but when utilizable nitrogenous compounds are present in relative abundance ammonia is liberated faster than it is consumed and masks the presence of the intermediate acid which is never present in large amounts. When the glycerol is used up before the nitrogen supply is depleted the culture remains alkaline. However, when the utilizable nitrogenous compound is relatively less abundant the nitrogen supply becomes depleted before

the glycerol supply and a point is reached where the ammonia remaining is insufficient to neutralize the small amounts of the intermediate acid being constantly formed and the culture becomes acid. Due to lack of ammonia, the bacteria can no longer proliferate, but if the pellicle remains afloat the organisms will continue to respire and continue to produce acid, so that the culture will remain acid until glycerol is exhausted. The pH value of the culture may then again rise due to the utilization of the anions of salts of organic acids.

SUMMARY

Studies were made of the growth, metabolism and tuberculin production of cultures of *M. tuberculosis*, human type, PN strain, on media containing different proportions of glycerol and of nitrogen from different sources, chiefly asparagine, glycine and the ammonium salts of glutamic, malic and malonic acids. The following are the more significant findings:

1. The production of acid was related to the proportion of glycerol present and to the source and proportion of nitrogen, but not to the amount of growth, nor to the rate of growth, nor to the amount of glycerol consumed.

2. On media containing nitrogen at high levels cultures always became alkaline during the earlier stages of growth when nitrogen was derived from asparagine, glycine, ammonium malate or ammonium glutamate. On malonate media under like conditions cultures first became acid, then, as the glycerol supply was depleted, the pH values tended to rise.

3. With the five sources of nitrogen mentioned, a definite relation was found between the glycerol:nitrogen ratio of the medium and the final reaction of the culture; the higher the ratio, the more acid the culture tended to become.

4. With each of the five sources of nitrogen, the yield of bacteria obtained was dependent on but not proportional to the amounts of glycerol and nitrogen present. Yields approximating 2.0 g. bacteria, dry weight, per 100 cc. medium were obtained from each source. Under favorable conditions yields of 10.0 g. of bacteria were obtained from each gram of nitrogen, but under no conditions did the yield exceed 0.38 g. bacteria per gram glycerol.

5. In media containing available nitrogen at high levels the glycerol supply was exhuasted about the time maximum weight was reached; at low levels, glycerol continued to disappear after the bacteria stopped increasing in weight.

6. The nitrogen metabolism of the organism was studied in cultures on asparagine media. When such cultures became acid the fall in pH value occurred about the time that the filtrate nitrogen was reduced to a minimum. No consistent relation was detected between the final pH value and residual ammonia in the filtrate.

7. Potent tuberculins were obtained from cultures grown on media in which nitrogen was supplied by any of the five sources of nitrogen mentioned.

The conclusion was reached that the nitrogenous constituents of the medium are the chief source of the alkali and that glycerol is the chief source of acid, which is probably produced as an intermediate oxidation product and is in turn further oxidized.

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INTRACUTANEOUS TUBERCULOSIS IN RABBITS[1]

Effect of Previous Injury on Lesions of the Primary and Secondary Type

WILLIAM H. FELDMAN AND FRANK C. MANN

The so-called phenomenon of Koch remains one of the most interesting and complex events associated with the response of the tissues to the tubercle bacillus. Experimentally, with few exceptions, the procedures followed to demonstrate the course of events initiated by reinfection with tubercle bacilli have consisted of introducing the infective bacteria subcutaneously. However, some years ago Krause and Peters, Krause and Willis, and more recently Sewall and Duffner, using guinea pigs, injected the reinfecting agents intracutaneously. The description of the morbid changes that followed was limited for the most part to an account of the alterations that occurred macroscopically.

That information might be obtained concerning the response of the skin to experimental infection with tubercle bacilli, a study was made in which the infective bacteria were injected intracutaneously into normal and into previously sensitized rabbits. The study was planned so as to provide, for examination, morbid changes in response to the tubercle bacillus under a diversity of conditions. These conditions were briefly as follows: (*1*) the previously unaltered skin of normal rabbits; (*2*) the previously unaltered skin of sensitized rabbits; (*3*) the skin of both normal and sensitized rabbits previously altered by trauma and by the intracutaneous injection of old tuberculin.[2]

[1] From the Division of Experimental Medicine, The Mayo Foundation, Rochester, Minnesota.

[2] The idea of studying the influence of an acute unspecific inflammatory process on the subsequent development of a tuberculous infection initiated in the damaged tissues was mentioned many years ago by Krause and Willis. Although Krause and Willis reported on the effects following the intracutaneous reinfection with virulent tubercle bacilli of the site of the local reaction to tuberculin, they did not observe the effects following the injection of tubercle bacilli into local regions of the skin that had been damaged physically by thermic, chemical or traumatic means. Their failure to make this observation was due to the apparent inability to secure "an inflammation, the physical extent and character of which were at all comparable to those of the inflammation of the tuberculin skin reaction." In 1932, Klopstock, Pagel and Guggenheim reported a study in guinea pigs on the influence of a local allergic inflammation on the defense of tissues against injection of tubercle bacilli. The local inflammation was

METHODS

Group 1. Sensitized rabbits: A group of 10 adult rabbits of comparable size and age were injected subcutaneously with 0.1 mg. of a sixty-six day old subculture of a pathogenic strain of bovine tubercle bacilli.[3] Forty-four days later the hair was removed over a considerable portion of the back with an electric clipper. On that portion of the back where the hair had been removed, three areas about 3 cm. in diameter in tandem formation were circumscribed with an indelible pencil. Twenty-four hours after the hair had been clipped there was injected intracutaneously into the most anterior of the three circumscribed regions 0.02 cc. of a 1:100 dilution of Old Tuberculin.[4] Twenty-four hours after the injection of tuberculin the skin in the circumscribed area occupying the middle position was subjected to trauma.[5] Forty-eight hours after the injection of tuberculin and twenty-four hours after the skin of the middle

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induced by several injections of atoxyl diazotate and twenty-five days later by injecting simultaneously tubercle bacilli and atoxyl diazotate intracutaneously. An equal number of nonsensitized guinea pigs were similarly treated. The changes were studied histologically and the authors concluded that the changes in the sensitized animals appeared to be accelerated and more severe than in the nonsensitized controls. However, there was no difference in length of life in the two groups.

[3] The organism had been isolated four months previously from a tuberculous lymph node of a bovine animal.

[4] All of the animals subsequently showed a definitely positive reaction to tuberculin twenty-four and forty-eight hours after the injection of this product.

[5] The trauma was accomplished while the animal was under ether anaesthesia by attaching to the skin for one minute a heavy pair of compression forceps. The method followed in our study to inflict damage to the tissues seemed to result in a definite injury. However, it is not claimed that such a region of damaged tissue is in any way comparable to the local reaction that follows the intracutaneous reaction to tuberculin in a sensitized animal. In fact the reaction to trauma in such a region is definitely dissimilar to that resulting from the intracutaneous injection of tuberculin. Information on the character of the changes that followed traumatizing of the skin was obtained by securing material for biopsy from five nontuberculous rabbits, the skin of which had been subjected to trauma twenty-four, forty-eight and seventy-two hours previously. A total of twelve biopsy specimens were studied. The local reactions, twenty-four hours after the region was traumatized by the heavy compression forceps, were found not to vary essentially in the several specimens examined. It was noted that the fibres of the *pars reticularis* were distorted and widely separated by oedematous fluid. There was a moderate infiltration of polymorphonuclear leucocytes and a somewhat smaller number of monocytes or histiocytic forms. In a few instances there was noted a small amount of haemorrhage. The muscle of the subdermal zone showed a shattering of some of the fibres and a loss of substance in some instances. This was the character of the site into which tubercle bacilli were injected intracutaneously to determine what effect, if any, a nonspecific inflammatory reaction might have on the subsequent behavior of the tissues toward the specific infective agent.

area had been traumatized, each of the three regions—the site of the tuberculin reaction, the region of trauma and the most posterior region which had not previously been disturbed—was injected intracutaneously with 0.002 mg. of a freshly prepared suspension of bovine tubercle bacilli representing the same strain used to make the primary inoculation forty-seven days before. After the injection of the tubercle bacilli the rabbits were observed at frequent intervals and the local reactions recorded.

After the injection of tubercle bacilli, the 10 rabbits were killed as follows: one, after twenty-four hours; one, after forty-eight hours; one, after three days; one, after five days; one, after ten days; one, after seventeen days; one, after twenty-four days; one, after thirty-one days; one, after thirty-eight days; and one, after forty-five days. At the time of death, that portion of the skin embracing the three regions into which tubercle bacilli had previously been injected was removed for subsequent histological study. Duplicate sections were made from each block. One was stained with haematoxylin and eosin and the other with a Ziehl-Neelsen combination to reveal acid-fast bacteria.

Group 2. Nonsensitized rabbits: Group 2 consisted of 10 apparently normal rabbits of comparable size and age to those composing group 1. The hair was removed from a large area of the back, and three sites for subsequent injections were circumscribed with an indelible pencil. On the same day that tuberculin was injected into the most anterior of the prepared sites in the rabbits in group 1, the same procedure was followed in group 2.[6] Subsequent procedures were identical in both groups with the exception that the animals in group 2 were permitted to live until they died from tuberculosis. In this group the regions of the back where tubercle bacilli had been injected were removed surgically with the animals under ether anaesthesia. Sections were prepared as previously mentioned for histological study.

At the termination of the experiment there was available from sensitized and nonsensitized rabbits material representing the changes that had occurred in altered and nonaltered regions of the skin from one to forty-five days after the infective agent had been introduced.

RESULTS

The pertinent changes noted and the differences, if any, that were recognized in the lesions under the different conditions imposed, follow.

[6] None of the animals in group 2 reacted to tuberculin prior to the intracutaneous injection of tubercle bacilli.

Local reactions twenty-four hours after injection of tubercle bacilli: In the nonsensitized rabbit no demonstrable reaction occurred except in the region that had previously been traumatized. The reaction in this instance was that associated with the usual inflammatory changes and was characterized by the occurrence of considerable oedema and polymorphonuclear leucocytes, histiocytes and macrophages. In the sensitized rabbit the situation was strikingly different. Each of the three regions where the bacilli had been injected was the site of a definite and vigorous cellular response. The reaction consisted of polymorphonuclear leucocytes and foci of histiocytic forms and evidence of early or beginning necrobiosis. Except for the tissue damage that had resulted from the episode of trauma, the reaction in each of the three regions was essentially similar and had a significant resemblance to that induced by the injection of tuberculin into the skin of sensitized animals.

Local reaction forty-eight hours after injection of tubercle bacilli: In the nonsensitized rabbit there were no striking macroscopical differences in the different regions of reaction. Each of the three regions showed a small amount of induration with no erythema. Microscopically the changes, which were of moderate severity, consisted essentially of a marked infiltration of polymorphonuclear leucocytes, some oedema and a few histiocytes. A few acid-fast bacteria could be seen. In the sensitized rabbits, the reaction was much more severe although the character of the cellular response was similar to that in the lesions of the nonsensitized animal. The respective sites where the tubercle bacilli had been injected were definitely reddened and induration was evident. The region where tuberculin had previously been injected showed the beginning of an abscess in the central portion of the dermis (figure 1). This abscess was composed largely of polymorphonuclear leucocytes.

Local reaction three days after injection of tubercle bacilli: Grossly erythema was present in each of the three series where tubercle bacilli had been injected into the skin of the nonsensitized rabbit and the skin of the sensitized rabbit. There was, however, one difference in the reactions in the rabbit that had been sensitized previously, in that in addition to erythema each region was also indurated.

The differences in the reactions in the nonsensitized and in the sensitized rabbits were more striking microscopically than grossly. The reactions that occurred in the nonsensitized rabbit were of minimal severity with polymorphonuclear leucocytes predominating in the region that had been previously injected with tuberculin and in the region that had been traumatized (figure 2). The reaction in the unaltered region was mostly histiocytic in character with a moderate number of polymorphonuclear leucocytes present. In none of the lesions of the nonsensitized rabbit was necrosis a marked feature. In the sensitized rabbits the appearance of the lesions indicated a reaction of severe character. The reactive process occupied the entire width of the dermis and

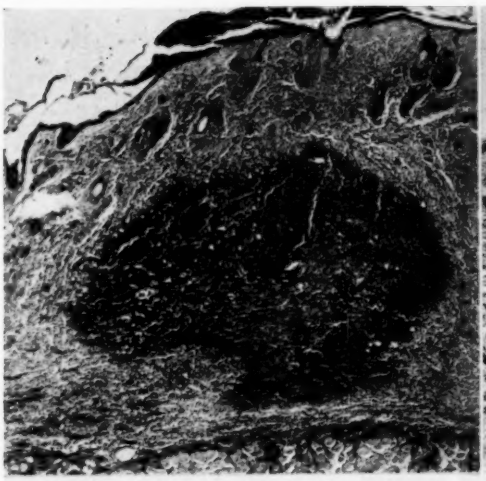

FIG. 1

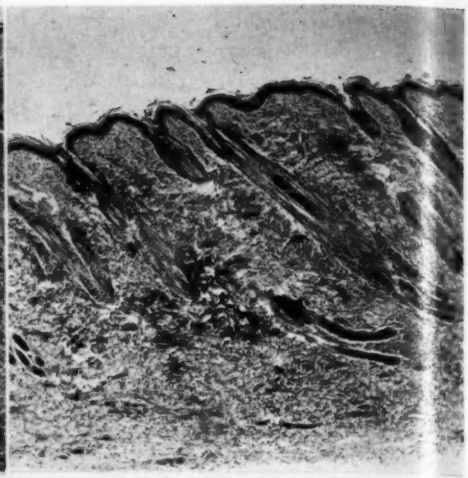

FIG.

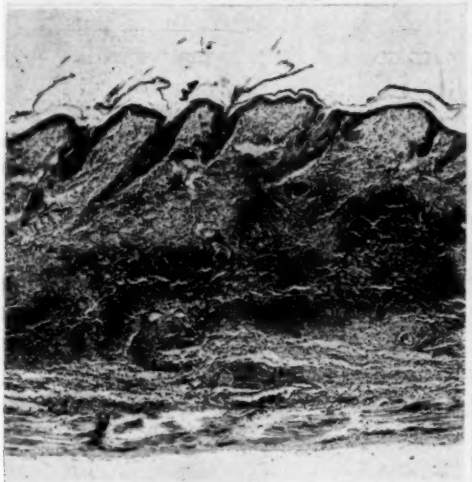

FIG. 3

FIG.

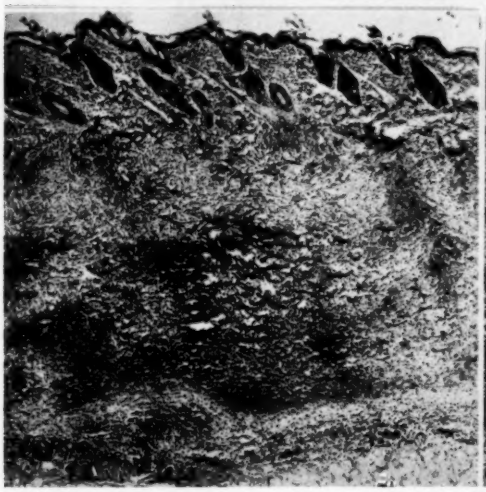

FIG. 5

FIG.

FIGS. 1–6

necrobiosis was a striking feature (figure 3). There was a vigorous histiocytic response and a moderate number of polymorphonuclear leucocytes. Many of the latter showed signs of early necrosis. Some oedema and haemorrhage were noted, the haemorrhage being especially evident in the region where tuberculin had previously been injected. Only a few acid-fast bacteria were noted. Regions of softening or beginning abscess formation were observed in both of the sites that had previously been altered; one with tuberculin and the other by trauma. It was clearly evident that the reaction in the skin of the sensitized rabbit was much more severe than in the skin of the nonsensitized animal and that the most severe changes occurred in the regions where the tissues had experienced previous alterations due to the Old Tuberculin and to the trauma.

Local reactions five days after injection of tubercle bacilli: Grossly all situations where tubercle bacilli had been injected showed erythema. In both rabbits the site where tubercle bacilli had been injected into the previously unaltered tissue showed the most pronounced redness. All of the local lesions in the sensitized rabbit were indurated. Comparing the lesions microscopically in the two rabbits it was at once apparent that the most vigorous reactions had occurred in the three lesions from the rabbit that had been sensitized. The lesions were larger, there was more softening and other evidence of necrobiosis and oedema was a more constant feature (figures 4 and 5). Histiocytes were prominent in the lesions of both rabbits and in the lesions of the sensitized animals early formation of tubercle was observed at the periphery of the irregular necrotic foci. Most of the polymorphonuclear leucocytes had either succumbed to the necrobiotic changes or showed evidence of early necrosis such as pyknosis. Acid-fast bacilli were extremely scarce in all of the lesions.

Local reactions ten days after injection of tubercle bacilli: Grossly there was considerable difference between the lesions in the nonsensitized rabbit and those of the sensitized animal. Two of the lesions from the former showed

FIG. 1. Abscess formation in the dermis forty-eight hours after reinfection with bovine tubercle bacilli. The region had been injected ninety-six hours previously with Old Tuberculin. × 18

FIG. 2. Minimal reaction in the dermis three days after bovine tubercle bacilli had been injected into region that had previously been traumatized. Primary infection. × 18

FIG. 3. Severe necrotizing lesion in the previously traumatized dermis, three days after bovine tubercle bacilli had been introduced. Reinfection. (Compare with figure 2.) × 18

FIG. 4. Small focus of necrosis in the dermis five days after the injection of bovine tubercle bacilli into a region that had been previously subjected to trauma. Primary infection. × 18

FIG. 5. Marked reaction with considerable necrosis in the central portion of the dermis five days after injection of bovine tubercle bacilli. Region had previously been traumatized. Reinfection. × 18

FIG. 6. Extensive involvement of the dermis in region of previous trauma ten days after injection of bovine tubercle bacilli. Primary infection. × 18

FIG. 7

FIG. 8

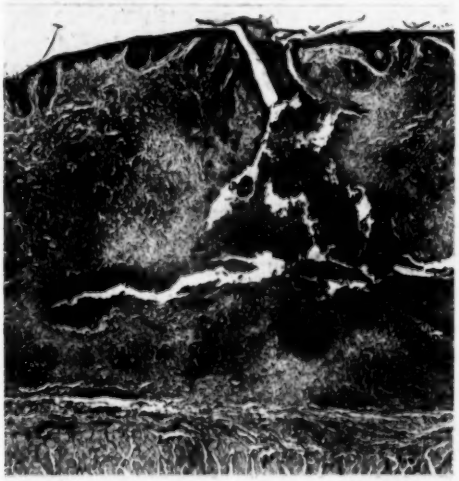

FIG. 9

FIG. 10

FIG. 11

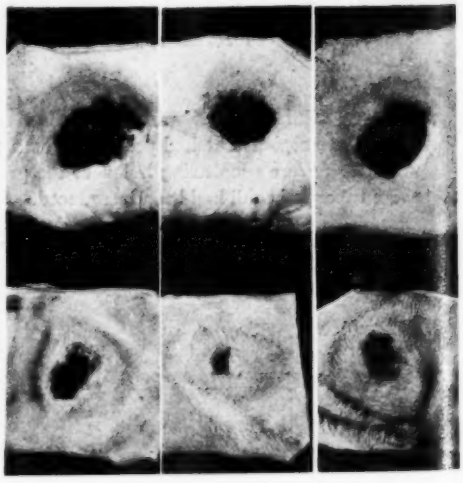

FIG. 12

FIGS. 7–12

dry, crater-like ulcerations and the third, in the region where tuberculin had previously been injected, was markedly reddened and swollen. None of the lesions in the skin of the sensitized rabbit had ulcerated, although microscopically it was apparent that erosion of the epidermis would not have been long delayed. Microscopically the changes in the lesions of both rabbits were essentially similar, consisting of extensive foci of necrosis in the central portions of the dermis (figure 6). The softened necrotic foci were surrounded by a considerable number of histiocytes which in the case of the lesions from the previously sensitized rabbit were becoming epithelioid in character. In the sensitized rabbit there was perhaps a greater tendency for early formation of tubercle at the periphery. Some peripheral fibrosis was evident in all of the lesions. Eosinophilic granulocytes were numerous throughout, being especially abundant in the necrotic debris. No acid-fast bacilli were seen in any of the lesions.

Local reaction seventeen days after injection of tubercle bacilli: Grossly the lesions from the nonsensitized rabbit seventeen days after infection did not appear greatly different from those obtained from the nonsensitized rabbit on which biopsy had been performed ten days after the infective agent was introduced. The lesions were about 1 cm. in diameter and the lesion that developed at the site where tuberculin had been injected previous to infection showed a small sharp-edged pit. The region that had been traumatized was reddened and the margin was indefinite. The third lesion where the threshold had not been altered previous to the injection of tubercle bacilli had a dry scab

FIG. 7. Severe reaction of the dermis with marked softening seventeen days after injection of bovine tubercle bacilli in the region of previous traumatization. Primary infection. × 18

FIG. 8. Portion of the dermis of previously sensitized rabbit seventeen days after injection of traumatized region with bovine tubercle bacilli. There are present considerable epithelioid reactions and a few foci of caseation necrosis. (Compare with figure 7.) × 18

FIG. 9. Central necrosis with peripheral zone of activity in the dermis twenty-four days after intracutaneous injection of bovine tubercle bacilli into the region where Old Tuberculin had been introduced prior to the inoculation of the bacilli. Primary infection. × 18

FIG. 10. Extensive slough of epidermis and the upper portion of the dermis twenty-four days after the injection of bovine tubercle bacilli into the region of previous tuberculinization. Most of the necrotic debris has been evacuated. Reinfection. × 18

FIG. 11. Advancing tuberculosis of the dermis with diffuse regions of caseation necrosis and erosion of the epidermis thirty-eight days after the intracutaneous injection of bovine tubercle bacilli in the region where Old Tuberculin had previously been introduced. Primary infection. × 18

FIG. 12. Tuberculous lesions of the skin of two rabbits forty-five days after the intracutaneous injection of bovine tubercle bacilli. The three lesions in the top row represent primary infections while the three lesions in the bottom row represent reinfections. Considered vertically, the two specimens in the first row represent regions into which Old Tuberculin had been injected prior to the infective agent; the two specimens in the middle row had been previously traumatized before tubercle bacilli were introduced; and the site of the infections in the two specimens in the third row was unaltered prior to inoculation with tubercle bacilli.

in the centre of the area of reaction. The lesions in the sensitized rabbit appeared grossly to be more or less quiescent.

Microscopically considerable differences were noted in the lesions of the two rabbits. Those of the nonsensitized animal contained large irregular regions of softening occupying the central portions of the dermis (figure 7). The intact portion of the lesions at the periphery consisted of histiocytes, large numbers of eosinophilic granulocytes and a few lymphoid forms. Only a few epithelioid cells were apparent. Arteritis and other endovascular changes were noted in some of the blood vessels on the outer zone of the lesions. Neither acid-fast bacteria nor giant cells of the Langhans type were observed.

Generally speaking the lesions in the nonsensitized rabbit represented a severe necrotizing or purulent reaction in which an advancing tuberculous process was persisting at the margin of the necrotic regions.

Histological evidence revealed that the changes in the lesions of the previously sensitized rabbit were less severe and of a somewhat different character from those of the nonsensitized rabbit killed on the same day. With the exception of the region that was previously unaltered, which showed a purulent softening of the central portion of the dermis, the lesions of the sensitized rabbit were intact although they contained a few foci of caseation necrosis (figure 8). The peripheral zone of the lesions consisted of epithelioid tubercles or a diffuse tuberculogenic region of diffusely disposed epithelioid cells. The severe necrotizing effect that characterized the lesions of the nonsensitized rabbit was not evident in the sensitized rabbit. Remnants of polymorphonuclear leucocytes and numerous eosinophilic granulocytes were present among the epithelioid cells. Acid-fast bacteria or Langhans' giant cells were not seen.[7]

Local reaction twenty-four days after injection of tubercle bacilli: Grossly, crater-like ulcers were noted in the nonsensitized rabbit in the regions where previously tuberculin had been injected and trauma inflicted. A small amount of creamy exudate was escaping from the lesion that had developed in the region that previously had been unaltered. The lesions in the skin of the sensitized rabbit all measured about 1 cm. in diameter and were more or less flattened and each contained a dry ulcer with rather sharp edges.

Microscopically each of the three lesions of the nonsensitized rabbit was essentially similar to the others. These were characterized by an advancing

[7] Considering the changes that were noted in the sensitized rabbits killed ten days and twenty-four days respectively after the intracutaneous injection of tubercle bacilli, the lesions observed in the sensitized rabbit after seventeen days seem less severe than one might have expected. The rabbit from which the seventeen-day old reactions were obtained was definitely tuberculous when examined at necropsy the day the lesions of skin were removed.

destructive necrosis and softening of the central portion of the infected region. Histiocytes, some showing mitosis, were numerous in the zone between the necrotic foci and the intact dermis. A considerable number of epithelioid cells occurred in the lesions of each of the three regions and eosinophilic granulocytes were numerous throughout. There was but slight tendency toward formation of tubercle. No giant cells of the Langhans type or acid-fast bacilli were noted. All of the lesions showed erosion of the epidermis. The epidermis and much of the underlying dermal tissue of the sensitized rabbit had sloughed out leaving a widely exposed ulcerated surface. The character of the cellular response in the tissue that remained intact was predominantly epithelioid with a marked tendency toward the formation of tubercles. Eosinophilic granulocytes were numerous among the epithelioid elements and an occasional giant cell of the Langhans type was seen. Acid-fast bacteria, however, were not noted.

Contrasting the lesions of the nonsensitized rabbit with those of the rabbit that was sensitized, the most significant difference was the severity of the necrobiotic changes that persisted in the lesions of the rabbit that was not sensitized previously by the intracutaneous injection of tubercle bacilli (figure 9). In this rabbit the necrotic changes were advancing apace with the progression of the infection while in the sensitized rabbit the major effect of the necrosis had been exerted previously and the debris had been exuded through the ulceration at the surface (figure 10). The reaction to the infection continued in this rabbit but without much, if any, of the accompanying necrosis that was so strikingly evident in the lesions of the nonsensitized rabbit.

Local reaction thirty-one days after injection of tubercle bacilli: Grossly each of the three lesions in the skin of the nonsensitized rabbit contained a dry pit-like ulcer varying from 0.5 to 1.3 cm. in diameter. The surface of the lesions in the sensitized rabbit was apparently intact but there was present on the surface of each a small dry scab.

Microscopically the changes in each of the three lesions from the nonsensitized rabbit were similar. The lesions were characterized by the involvement of the entire width of the dermis and of the underlying layer of muscle. The lesions were of a soft necrotizing character with a broad peripheral zone of epithelioid cells, histiocytes and few to a moderate number of eosinophilic granulocytes. Although there were many foci and diffuse regions of necrosis among the epithelial cells of the peripheral portions of the lesion, the tuberculous process was advancing and showed other evidence of progression. Acid-fast bacteria or Langhans' giant cells were not observed.

The histological picture of the lesions from the previously infected rabbit was in some respects dissimilar to what one might expect the lesions of reinfection to be. The lesions were characterized by a severe, wide-spread necrosis

that resembled the reaction to primary infection.[8] The necrosis was that of early caseation. At the margin of the lesions there occurred a narrow zone of histiocytes. Epithelioid cells were few as were epithelioid tubercles. Giant cells of the Langhans type were not seen, nor were acid-fast bacteria observed. The extensive and severe necrosis and the relative paucity of epithelioid cells were the important features of the lesions in this instance. That complete erosion of the epidermal layer and subsequent evacuation of the necrotic debris had not occurred is worthy of note and suggests that a measure of inhibition not present in primary infection was operative in this instance.

Local reaction thirty-eight days after injection of tubercle bacilli: Grossly the lesions of the nonsensitized rabbit were essentially alike. All were about 1 cm. in diameter and the surface of each showed dry ulcers having a "punched-out" appearance. The lesions of the previously sensitized rabbit were rather flat in relation to the surface of the surrounding skin. In diameter they measured at the greatest dimension between 0.5 cm. and 1.2 cm., the smallest being the lesion that developed in the region that had been traumatized. Each of the lesions showed erythema and a small scab formation.

Microscopically no significant differences were noted in the three lesions of the nonsensitized rabbit. The process was that of an active and advancing tuberculosis accompanied by a considerable amount of caseation necrosis and some purulent exudate at the surface. Histiocytes and epithelial cells predominated in the regions of activity (figure 11). Many eosinophilic granulocytes were also present. Single and conglomerate tubercles were noted. A definite fibrosis was evident in the regions of the epithelioid reaction. Neither giant cells of the Langhans type nor acid-fast bacilli were observed.

Each of the lesions of the previously sensitized rabbit showed a definite tendency to heal as evidenced by the minimal amount of necrosis, the epithelioid character of the cellular response and the inclination toward fibrosis. While it is true that extensive erosion of the epidermal layer had occurred, the cavities previously formed by the evacuation of the necrotic tissues of the dermis were being filled by a "hard" tuberculous process that was quite dissimilar to the state of affairs in the lesions of the previously nonsensitized rabbit. In the sensitized animal the infective process had diminished in its destructiveness and a measure of repair was in progress. In the nonsensitized rabbit, although the reaction showed some fibrosis, it continued to be progressive and necrotizing. Several giant cells of the Langhans type were present in the lesions of the sensitized rabbit but acid-fast bacillary forms were not observed. Relatively few eosinophilic granulocytes occurred.

[8] At necropsy of this rabbit, at the time the lesions of the skin were obtained, there was present an extensive tuberculosis of the lungs, subserous foci along the intestine and tuberculous adenopathy of the axillary lymph nodes.

Local reactions forty-five days after injection of tubercle bacilli: Grossly the three lesions in the skin of the previously nonsensitized rabbit and those in the skin of the rabbit that had been sensitized prior to the intracutaneous injection of tubercle bacilli were essentially similar to each other (figure 12). They measured approximately 1.3 cm. in diameter and with one exception all of the lesions contained at the surface a dry pit-like ulcer. The exception was the lesion in the region of the skin of the sensitized rabbit that had been traumatized previously. In this instance a small dry scab occurred at the surface of the lesion.

Microscopically each lesion of the previously nonsensitized rabbit was characterized by an extensive erosion of the epidermis with caseation necrosis of the exposed portions of the lesion and progression of the lesion laterally with slight evidence of limiting inhibitions. Histiocytes were numerous and showed, in some regions, a tendency to yield epithelioid forms. Large numbers of eosinophilic granulocytes were present as were a few giant cells of the Langhans type. Acid-fast bacteria were not seen. To reiterate briefly, the morbid process consisted of an aggressive necrotizing tuberculosis in which destruction and progression were equally important.

Each lesion in the skin of the previously sensitized rabbit showed a loss of the epidermal layer, necrosis of the connective tissue of the more superficial portion of the dermis and a zone of intact histiocytes and fibroblastic activity in the lower third of the involved dermis. In the depths of the lesions striking endovascular changes were noted. These consisted of endarteritis, periarteritis and thrombosis. Numerous acid-fast bacilli were observed in the debris of the superficial ulcerations. No giant cells were seen.

Although the forty-five day old intracutaneous lesions of the two rabbits were not markedly dissimilar to each other there were a few distinguishing features that were significant. The progression evident in the periphery of the lesions of the nonsensitized rabbit was less impressive in the lesions of the rabbit that had been previously sensitized. Furthermore, in the latter, fibrosis was an important feature of the reaction and the amount of caseation necrosis was considerably less than in the lesions of the nonsensitized rabbit.

COMMENT

Except for the factor of sensitivity, the results of this study failed to indicate that previous alterations of the threshold of infection influenced significantly the subsequent course of the local reaction to the tubercle bacillus. It was observed fairly consistently that the severity of the tuberculous process in each of the three regions of intracutaneous infection was essentially the same whether the bacteria had been intro-

duced into the site of the previous injection of tuberculin, the site of previous trauma or the site where the tissues had previously been unaltered locally.

Our results might at first seem to be in conflict with those obtained many years ago by Krause and Willis. These authors studied the reinfection of sensitized guinea pigs injected intracutaneously with virulent tubercle bacilli into the region where the skin had previously reacted to a watery extract of tuberculoprotein. They concluded that in tuberculous guinea pigs sensitization and immunity are reduced within the region of the local inflammatory reaction to tuberculin for at least four days after the injection with tuberculin. They also found sensitization and immunity to be reduced to a greater extent within the first twenty-four to forty-eight hours after the injection of the tuberculin than later.

Our experiment and that of Krause and Willis were basically unlike. We were interested in knowing what effect if any the local inflammatory reaction to tuberculin and the local inflammatory reaction to injury induced by trauma might have on the inception and subsequent development of the local lesions and we more or less disregarded dissemination of the infective agent to other parts of the body. In other words, we were concerned with the primary lesions that developed in altered skin while Krause and Willis were concerned with the amount of tuberculosis present at necropsy in previously sensitized guinea pigs that had been reinfected by the injection of virulent tubercle bacilli into the region where a local reaction to tuberculin was manifest.

We anticipate the criticism that the number of animals utilized in our study should perhaps have been larger and that provision should have been made to provide material for longer periods of observation. These points, though pertinent, do not, we believe, invalidate seriously the general conclusions that the results indicate.

Our observations supply data that permit the reiteration of the fact that in the sensitized rabbit the immediate local cellular reaction to viable tubercle bacilli is not essentially unlike the local response to tuberculin. Eventually of course marked differences appear, the most important being that the intracutaneous injection of tubercle bacilli induces a progressive tuberculous lesion while the effects from tuberculin are less destructive and of shorter duration and are eventually reversible.

The results of this study also demonstrate the fact, which has been shown by others, that the phenomenon of Koch can be followed as

satisfactorily in the skin as in the subcutis or can even be followed more satisfactorily in the former than in the latter.

That there may be individual variations in the local tissue reactions to reinfection is suggested by the results noted in the cutaneous lesions obtained from the previously sensitized rabbit, thirty-one days after reinfection. Although in this instance some evidence of resistance not present in the tissues of the nonsensitized rabbit was suggested, the marked necrotizing character of the changes and the relatively few epithelial cells present were indicative of a process that was more progressive than one might expect if the usual degree of resistance or immunity were operative.

SUMMARY AND CONCLUSIONS

The character of the local response to virulent bovine tubercle bacilli injected intracutaneously into rabbits was studied. Two groups of 10 rabbits each were utilized, one group not previously infected and one group sensitized by the subcutaneous injection previously of the same strain of tubercle bacilli used to make the subsequent intracutaneous inoculations. Tubercle bacilli were injected into the skin of three different regions of the back of each rabbit. Into one of these regions tuberculin had been injected forty-eight hours before the tubercle bacilli were introduced. Another of the regions was traumatized twenty-four hours before the infective agents were injected while the third region into which tubercle bacilli were injected was previously unaltered.

The lesions of the skin from one animal in each group were obtained for histopathological study at various intervals of time from one day up to forty-five days. It was found that (*1*) neither trauma nor the previous tuberculinization of a region influenced significantly the subsequent course of the resultant dermal reaction to tubercle bacilli as determined by a comparison of the local tissue alterations and cellular response; (*2*) the changes noted in the intracutaneous situations in the two groups of rabbits were essentially those one might expect in nonsensitized animals and in animals that were previously sensitized. In the first instance the process was that of primary infection; in the second the process was that which distinguishes the phenomenon of Koch.

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THE ERROR IN COUNTING BACILLI IN SPUTUM

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THE PROBLEM

Following is an attempt to apply the statistical technique of Student (1) to sputum counts in such fashion as, first, to make the interpretation of the count most useful, and, second, to obtain a picture of the distribution of bacilli on a slide under ideal conditions. Particular attention was paid to the study of the lower limit of detectability by direct microscopical examination of a smear.

In two previous publications, the writer (2, 3) showed how statistical methods together with standardized laboratory procedure could assist in the interpretation of results in immunity tests. These two—statistical method and standardized laboratory procedure—if applied to the sputum count, would probably prevent the multiplication of confusing statements regarding the limits of detectability. Confidence might be restored in the value of the sputum count in prognosis. Statistical aspects of the sputum count have received little attention since the publication of the classical paper *On the Error of Counting with a Haemocytometer* by Student (William Sealy Gosset, 1876–1937) in 1907.

Student showed that, when a haemocytometer was filled with a freely flowing suspension of yeast cells, these did not distribute themselves uniformly over the squares. He counted the numbers of haemocytometer squares having 0, 1, 2, 3, etc. yeast cells. From these data he found that the actual distribution fitted the distribution calculated with the aid of Poisson's series of probabilities of the numbers of squares having 0, 1, 2, 3, etc. yeast cells.

Following are a few of the recent investigations in which the Poisson series of probabilities was found useful: Fisher (4), in determining whether colony counts on plates were obtained with satisfactory technique; Matuszewski, Supinska and Neyman (5), in determining the probability that a colony on a plate is a pure culture; Muench (6), in studies of counts of eggs of *Schistosoma mansoni* on single slides. In this present

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paper, the statistical technique of Student is reversed; the Poisson distribution of bacilli in a smear and in counts of 50 or more microscopic fields is assumed. These assumptions are safe, provided the single bacilli were moved freely over the slide, and the mean number of bacilli per field is small, about 10 or less.

DATA ON A SMEAR HAVING MEAN NUMBER OF BACILLI PER FIELD = 0.1

A smear, 5 cm.^{2} in area, was made on an imaginary slide, using 0.1 cc. of an aqueous suspension containing 33,333 single tubercle bacilli per cc. Since one field (7) is not far from 0.015 mm.^{2}, there are 3,333 bacilli distributed over 33,333 fields. From the Poisson series of probabilities, the following distribution was calculated: 30,161 fields with 0 bacilli in each field; 3,016 fields with 1 bacillus in each field; 151 fields with 2 bacilli and 5 fields with 3 bacilli in each field. This statistical description of the smear does not locate the different kinds of fields.

The same smear was now handed successively to 20 investigators without information regarding the mean number of bacilli per field, with the request that they make a count of 50 fields each. Sampling was done with the aid of Tippett's Random Sampling Numbers (8). With this set of numbers many samples can be easily drawn, much more rapidly than with marked cards, marbles or other devices which are sufficient for drawing a few samples.

> But the reader must remember that in taking hundreds of samples he must expect to find improbable samples or even runs of such samples; they will be in their place in the general distribution of samples, and he must not conclude, from their isolated occurrence, that Tippett's numbers are not random. ((8) p. viii)

Theoretically each of the above 20 investigators should have found 5 bacilli; the actual samples gave 4, 7, 9, 10, 5, 6, 5, 9, 1, 1, 4, 4, 5, 4, 4, 5, 1, 7, 10, 5. The range, from 1 to 10 bacilli found, results in reports ranging from 66,000 to 660,000 bacilli per cc. Obviously, counts of 50 fields could be improved by counting 100 or more. Table 1 shows two extreme distributions with 1 and 10 bacilli, together with a "perfect" count. Table 1 may be read: Investigator 17 counted 49 fields with 0 bacilli on each field; 1 field with 1 bacillus, etc. The "perfect" sample was calculated from the Poisson formula; it represents a true cross section of the entire smear of 33,333 fields.

The practical question is, what is the count for the entire smear? It

is of doubtful value to average two or three samples of 50-field counts because, first, the worker cannot tell whether the counts represent the widest range and, second, even with 3 or more counts, but no other aids, the worker cannot be certain what the other counts will be.

The uncertainty has been eliminated by the calculation of tables of "confidence limits" which indicate the other counts. Such a table has been calculated by Ricker (9) and is shown below, in slightly abbreviated and reworded form as table 2. Originally the table was calculated by Ricker as an aid in those cases where single counts only are available. This is an example by Ricker:

In the course of studies of hay fever infections, counts were made of the quantity of pollen in the atmosphere. In one test, pollen was filtered from 1 cc.

TABLE 1

Distributions of bacilli in counts of 50 fields out of 33,333

Mean number of bacilli per microscopic field = 0.1

NUMBER OF BACILLI IN 1 FIELD	NUMBER OF FIELDS COUNTED IN SAMPLE		
	Number 17	Number 19	"Perfect"
0	49	40	45.2
1	1	10	4.5
2	0	0	0.2
3	0	0	0
Total fields counted.....	50	50	50
Total bacilli found.....	1	10	5

of air, and the number of grains present counted as 45. What confidence may be placed in this estimate?... Adopting the 0.95 confidence coefficient and referring to the table... the abundance of pollen in the region sampled is probably between 33 and 60 grains per cubic centimeter...

Assuming that investigator 17, after having counted 1 bacillus in 50 fields selected at random, has no other figures available, he may turn to table 2. This states that when 1 bacillus is counted (see first column) there are 99 chances out of 100 that subsequent counts over the same number of other fields will be between 0 and 7 bacilli. Investigator 19 could conclude, after his count of 10 bacilli, that other counts will be between 4 and 21. An advantage in making 2 counts is that by noting where their confidence limits overlap ((9) personal communication),

TABLE 2

Adaptation of Ricker's table of confidence limits for Poisson frequency distributions

TUBERCLE BACILLI COUNTED	99 CHANCES OUT OF 100, OTHER COUNTS WILL BE BETWEEN		TUBERCLE BACILLI COUNTED	99 CHANCES OUT OF 100, OTHER COUNTS WILL BE BETWEEN	
	Lower limit	Upper limit		Lower limit	Upper limit
0	0.0	5	26	15	42
1	0.0	7	27	15	43
2	0.1	9	28	16	45
3	0.3	11	29	17	46
4	0.6	13	30	18	47
5	1.0	14	31	18	48
6	1.5	16	32	19	50
7	2.0	17	33	20	51
8	2.5	19	34	21	52
9	3.1	20	35	22	53
10	3.7	21	36	22	55
11	4.3	23	37	23	56
12	4.9	24	38	24	57
13	5.5	25	39	25	58
14	6.2	27	40	26	59
15	6.8	28	41	26	61
16	7.5	29	42	27	62
17	8.2	31	43	28	63
18	8.9	32	44	29	64
19	9.6	33	45	30	65
20	10.3	35	46	30	67
21	11.0	36	47	31	68
22	11.8	37	48	32	69
23	12.5	38	49	33	70
24	13.2	40	50	34	71
25	14.0	41	55	39	78
			60	43	84

TABLE 3

Showing distributions of bacilli in counts of 300 fields out of 33,333

Mean number of bacilli per microscopic field = 0.01

NUMBER OF BACILLI IN 1 FIELD	NUMBER OF FIELDS COUNTED IN SAMPLE		
	Number 3	Number 13	"Perfect"
0	299	293	297
1	1	7	3
2	0	0	0
Total fields counted.....	300	300	300
Total bacilli found.....	1	7	3

4 to 7 in this instance, one obtains a narrower range within which the theoretically correct number lies.

DATA ON A SMEAR HAVING MEAN NUMBER OF BACILLI PER FIELD = 0.01

A smear was prepared as before, using 0.1 cc. of an aqueous suspension containing 3,333 single bacilli per cc. There were, therefore, 333 bacilli distributed over 33,333 fields as follows: 33,002 fields with 0 bacilli on each field; 330 fields with 1 bacillus; 2 fields with 2 bacilli on each field. This distribution was calculated from the Poisson formula. Twenty investigators, without knowledge of the actual count, now made counts of 300 fields each. The reason for the counts of 300 is that counts of 50, 100, 150 and occasionally 200 fields failed to disclose a single bacillus when Tippett's random sampling numbers were used as a device for drawing samples. On the other hand, every count of 300 fields disclosed at least 1 bacillus. Theoretically, all 20 investigators should have found 3 bacilli; the samples gave 2, 4, 1, 2, 2, 3, 1, 6, 3, 6, 2, 1, 7, 4, 4, 3, 7, 2, 5, 2. Two extreme samples are shown in table 3, together with a "perfect" sample calculated from the Poisson formula.

Investigator 3, turning to table 2, of Ricker's confidence limits finds that his count of 1 bacillus means that other similar counts will be between 0 and 7 bacilli. Investigator 13 finds that his count of 7 bacilli means that other similar counts will be between 2 and 17. If both counts, on 300 fields each, were available to the same person, the true count for the entire smear could be placed somewhere within the overlap, 2 to 7. Working separately these workers would report 3,300 and 23,100 bacilli per cc. of sputum. Both are correct counts of 300 fields drawn at random from 33,333. Even with 300 fields as one count, some of the samples are poor when the mean number of bacilli per field is 0.01. Samples like number 13, or worse, will happen about once in a hundred samples.

DATA ON A SMEAR HAVING MEAN NUMBER OF BACILLI PER FIELD = 0.003

On an imaginary slide, a smear was made as before, 5 cm.^{2} in area, using 0.1 cc. of an aqueous suspension containing 1,000 single tubercle bacilli per cc. There were 100 bacilli on this slide distributed as follows: 33,233 fields with 0 bacilli, and 100 fields with 1 bacillus on each.

The slide was handed to 30 investigators each of whom made a count of 300 fields. Their reports, obtained with the aid of Tippett's random sampling numbers, are as follows: 0, 0, 0, 0, 1, 0, 1, 1, 0, 3, 0, 3, 3, 1, 0,

0, 0, 1, 0, 1, 1, 2, 1, 0, 0, 0, 1, 0, 2, 0. Since 16 out of 30 did not find a single bacillus, the count of 300 fields was not sufficient. With 100 single bacilli on the slide half of the reports will be "none found."

New counts were now made, each count being continued until one bacillus was found, then starting over again. Number of fields counted were: 1385, 606, 114, 684, 160, 34, 339, 195, 58, 138, 44, 43, 321, 1023, 707, 379, 224, 94, 145, 59, 1248, 407, 60, 816. In the first of these counts, a bacillus was found in the 1385th field; in the last count, in the 816th field. In 7 of these 24 counts the bacillus was not found until the count had continued beyond the 500th field.

The above mentioned 16 investigators who did not find a single bacillus could conclude, after consulting table 2, that other similar counts will range from 0 to 5 bacilli—a point on which clinical practice and statistical theory agree.

DISCUSSION

Confusing statements—usually not comparable—may be found in the literature regarding the limits of detectability of tubercle bacilli with the microscope. In a tuberculosis research laboratory, when counts of 500 fields were made on a direct smear of a negative sputum to which 50,000 bacilli per cc. had been added, none were found, although the slide had about 5,000 bacilli on it. If the foregoing statistical sampling and theory are correct, a few bacilli should easily have been found. (See page 352.) The "extinction point" in this laboratory is taken at 100,000 bacilli per cc. of sputum, or about 10,000 bacilli on a slide. In another laboratory it is taken at 1/100th of this limit or 100 bacilli on a slide. Such a slide would be reported "none found" in about half the examinations under ideal conditions. What the results are under actual conditions can be surmised.

A standardized technique for direct counting of the number of bacilli in 1 mg. of tubercle bacilli would be helpful. The figures range from 40 million by Calmette (10) to 11 billion by Chin kuk Choun (11). Future comparisons would be facilitated if, when the counts are made, a hundred bacilli were measured. In the dark field microscope, unstained single human tubercle bacilli are almost straight cylindrical rods, with rounded ends. No great error would be made in calculating their volumes as that of right cylinders. Given the numbers of the various sizes, the volumes could be easily calculated, and from this, the number per milligram. This would serve as a check on the direct count.

The statement that so and so many bacilli were added to a negative sputum leaves much to be desired regarding the certainty of the number added. This in turn complicates the problem of the laboratory determination of the limit of detectability, as well as comparative values of methods of concentration, flotation, etc.

CONCLUSIONS

From the statistical point of view, counting 50 or more fields in a sputum count consists in drawing a random sample from a population of 30,000 or more fields, which differ with regard to the number of bacilli on them.

Counts should be made by fields, not by minutes.

By statistical methods it was found that, when a slide has about 300 bacilli on it, a count of 300 fields always disclosed at least 1 bacillus. This is for ideal conditions.

The use of a table of confidence limits, in conjunction with the count, provides a better mental picture of the slide than the counts alone.

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BRIEF REPORTS

A SURVEY OF 2,854 TUBERCULIN TESTS[1]

A. M. PISCITELLI

The present survey is an attempt to show the trend of tuberculous infection among 2,854 children under fifteen years tested in the San Francisco Hospital Chest Clinic between 1927 and 1937. The children tested represent contacts (over half), those complaining of frequent colds, loss of weight, failure to gain, or those simply brought in for a physical examination. This group does not necessarily represent the poorest economic level in the city, though a good many were indigent. There are no financial restrictions for eligibility to the Chest Clinic since it is an undertaking of the Department of Public Health, and in an effort to find tuberculosis it is open to all applicants for purposes of diagnosis.

All children were given a Mantoux test with a 1:1000 dilution. A chest film was routinely made of all the positive reactors. A smaller proportion of negative reactors was also X-rayed for purposes of comparison.

RESULTS OF THE SURVEY

Of the 2,854 children tested 1,116, or 39.2 per cent, reacted positively; 46 per cent reacted positively in the eleven to fifteen year age group. Compared with the incidence at adolescence in various communities at different periods this shows a downward trend: for example, Vienna, 1909, 94.3 per cent positive tuberculin reactors; Graz, 1917–1921, 58 per cent; Minneapolis, 1926, 50.7 per cent. It is interesting to note however that the incidence in San Francisco, as compared with the findings of Dickey and Seitz (1) in 1925 to 1928, has not decreased. They found in adolescent clinic children a rate of 46.6 per cent.

1: Relation of positive tuberculin test to age: The incidence of positive reactors, as might be expected, varied proportionately to age: 32 per cent in the infant to five-year age group reacted positively; 38 per cent in the six to ten and 46 per cent in the eleven to fifteen age group.

2: Relation of positive tuberculin to sex: No relation was found between sex and positive tuberculin test. An almost equal percentage (38 per cent boys and 39 per cent girls) reacted positively.

[1] From the San Francisco Department of Public Health, San Francisco, California.

3: Relation of positive tuberculin to contact history: Fifty-eight per cent of the patients examined were contacts. The other 42 per cent were registered as "observation" cases. There was a higher, but not significantly higher, incidence of tuberculous infection among the contact group (41 per cent positive) than among the observation group (38 per cent).

4: Relation of positive tuberculin to X-ray findings: Nearly all (1,085) of the positive reactors were X-rayed; 587 negative reactors were also X-rayed. As is to be expected the group of positive reactors showed more intrathoracic lesions; 426, or 39 per cent, of this group showed some abnormality, but surprisingly enough 100, or 13 per cent, of the negative tuberculin group also showed some lesions. Of course some of these infiltrations might have been nontuberculous; or these patients may have belonged to that small group of persons in whom the tuberculous focus is completely healed or walled off from the blood-stream so that the tuberculin test changes from positive to negative.

Analysis of the 100 positive X-ray films in the negative tuberculin group showed that 71 (12 per cent) had calcified foci in the hilum lymph nodes; that 19 (3 per cent) had enlarged hilum nodes; that 3 patients had increased bronchial markings; that 3 had an interlobar effusion, one a basal tuberculosis and 3 a typical infiltration of the reinfection type. None of these patients had signs or symptoms of tuberculosis. The 3 with reinfection type were hospitalized for observation and after discharge have been carefully followed in the clinic. In the two to five years that have elapsed the patients have remained perfectly well. In no instance did a clinically positive (general symptoms and positive X-ray) tuberculosis give a negative tuberculin test.

Analysis of the X-ray films taken on 1,085 positive reactors showed: 659 (59 per cent) had no demonstrable lesion; 172 (15 per cent) showed typical tuberculous enlargement of the hilum nodes; 183 (16 per cent) showed "suggestive" enlargement; 67 (6 per cent) showed calcified foci in the hilum nodes; 4 (0.3 per cent) showed a reinfection minimal process at one or both apices.

5: Positive reactors in 1932 and 1937: Since many authors have pointed out the decline in positive tuberculin reactors within short periods of time, the number of positive reactors for the year 1937 was compared with the number for 1932. There was no difference: 37 per cent reacted positively in 1937 as against 36 per cent in 1932.

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PORTABLE PNEUMOTHORAX APPARATUS

J. G. ROSENBAUM[1]

Because of the high cost and weight as well as relative fragility of the present satisfactory pneumothorax apparatus offered on the market, an apparatus is presented which overcomes these objections.

The apparatus (figure 1), which has an overall size of 5¾″ x 12″ x 16″, weighs 9½ pounds when ready for use. It is housed in a plywood case, the exterior of which has two valve handles, the air outlet and a steel rod. Two recessed glass tubes are visible, one to indicate pressures in cm. of water, the other to indicate amount of air flow. No preparation is necessary for transportation—simply depress the rod and carry—there is no carrying case needed.

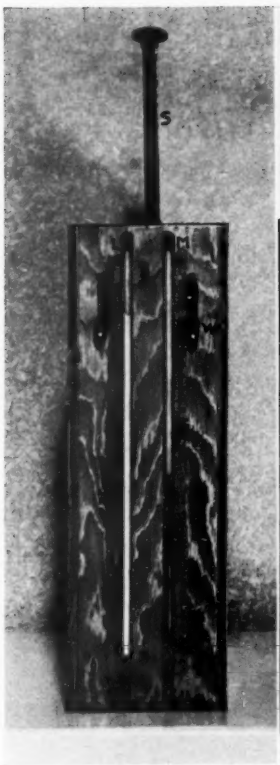
A side view of the apparatus is illustrated in figure 2. Figure 3 is a diagram which closely resembles figure 2. Two copper cans A and B are suspended by a continuous rope R through four pulleys P. The cans are connected at their bottoms by a rubber tube C. The water level in can A is indicated in glass tube L through its connection by means of rubber tube D. By raising rod S, can A goes up and B goes down. B which was empty, now begins to fill through tube C with water from can A. Air is displaced from can B and forced through rubber tube E past valve V and through tube K which runs to patient's chest. Volume flow is indicated on scale with tube L. To obtain a reading, valve V is closed, valve W to manometer opened. The author has found it preferable to leave valve W open at all times.

Colored water is used in manometer and cans. Water is added when necessary by pulling forward the tops of the glass tubes and injecting the required amount through a syringe.

For administration of air, the following procedure is observed:

1: Rod down, both valves on, water level at H.
2: Attach outlet tube to needle in pneumothorax space.
3: Close air valve V, take manometer reading.
4: Raise rod, fluid level rises to zero at top of tube L.
5: Turn air valve V on, fluid level in tube L drops indicating amount of air being injected. If manometer valve W is open, fluid in manometer will rise and fluctuate with respirations.
6: Close air valve, take manometer reading and remove needle.

[1] Mount Royal Sanatorium, Brecksville, Ohio.



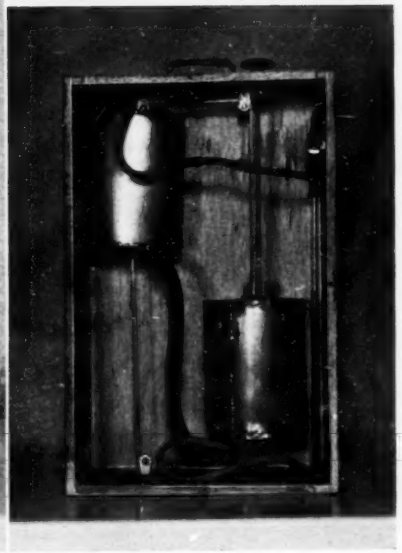


FIG. 1 FIG. 2

FIG. 1. Front view. Rod raised and ready for refill
FIG. 2. Side view, carrying position. Side wall removed

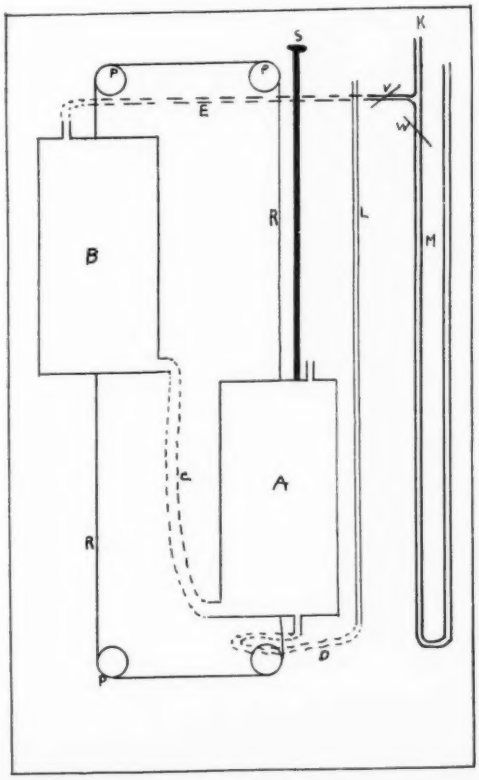


FIG. 3

7: Depress rod, turn valve on. When fluid level reaches H, apparatus is ready for next refill.

By reversing the process and using a two-hole stoppered flask as a trap, the apparatus is used for aspirations.

Advantages:

1. Easy administration without the need for a nurse. Chromium parts are sterilized by wiping with antiseptics.

2. Low weight and only recessed rubber padded glass tubing permit greatest ease in carrying.

3. Low cost. A local shop has made a number of these at a nominal price. They are now in use in various offices and hospitals in Cleveland.

The author wishes to thank Dr. N. S. Greene for his assistance and criticism.

CHRONIC NONTUBERCULOUS BASAL INFECTIONS OF THE LUNGS[1, 2]

LOUIS HAMMAN

The title of my communication lacks precision, and yet I can devise no more distinctive name for the group of cases I wish to draw to your attention. Moreover, this title and similar ones have previously been used to designate the condition from which these patients suffer, and to coin a new and unfamiliar term would add confusion to a situation already ill defined. To take words at their literal meaning, the title would include all inflammations affecting the lower lobes of the lungs excepting those due to tuberculosis, a long and heterogeneous list. As a matter of fact the title is often used to head medical articles which deal with all the diseases in the list, although usually of only one aspect of the diseases, most often the contrast between the clinical manifestations they produce and those caused by tuberculosis. I hope at once to put at rest any growing alarm you may feel about the possible length and range of my discussion by assuring you that I do not employ the title in this inclusive sense. To make clear the restricted sense in which I shall employ it I must review briefly how the term arose and to what use it has been put.

Working at the Phipps Tuberculosis Dispensary of the Johns Hopkins Hospital from 1905 to 1915, Doctor Wolman and I became deeply interested in a group of patients who at first confidently were thought to be suffering from pulmonary tuberculosis, but with the passage of years no definite proof of the tuberculous nature of their illness could be obtained. Only very gradually and reluctantly were we forced to concede that the original diagnosis was an error and that these patients did not have tuberculosis. There were certain characteristic symptoms common to them all and this led us to draw a clinical picture which we considered distinctive of the condition. These observations were presented briefly in 1916 before the National Association for the Study and

[1] Remarks made before the Buffalo Academy of Medicine, Buffalo, New York, February 8, 1939, and before the New York Academy of Medicine, New York City, April 21, 1939.

[2] From the Department of Medicine, Johns Hopkins University, Baltimore, Maryland.

Prevention of Tuberculosis and later they were published in the Transactions. We described the cardinal symptoms of the disease as follows:

1: All the patients had cough and expectoration which sometimes came on insidiously, sometimes followed an acute respiratory infection, grip, bronchopneumonia or an ordinary cold.
2: The symptoms in some patients were continuous, in others remittent or intermittent, but once begun they persisted indefinitely. Some of the patients had been under observation for eight years.
3: There was usually moderate, irregular fever, in some instances continuing uninterruptedly for years, at other times coming and going with the appearance and disappearance of cough and expectoration.
4: The only constant abnormality on physical examination was the presence of localized moist râles in one or both lower lobes of the lungs. These râles might be present constantly, always in the same location; or they might disappear with the subsidence of cough, to appear again at the onset of a fresh cold, always reappearing at exactly the same location where they had been present before.
5: In spite of the long continuation of cough, expectoration and fever the patients showed none of the symptoms of intoxication characteristic of tuberculous infections. Except for local symptoms they felt well, they did not lose weight, they did not complain of weakness or exhaustion.

We designated this condition as Chronic Nontuberculous Pulmonary Infection. The term is descriptive and its meaning obvious, though perhaps misleading, since it might be understood to include all chronic nontuberculous infections of the lung. Inasmuch as the lesions are almost invariably located in the lower lobes this important fact was later incorporated in the title by adding basal, or as some have it, basic.

Prior to the publication of our brief account the condition had been observed and commented upon by Lord. In 1902 and again in 1905 he described certain infections of the lungs due to the influenza bacillus which were frequently mistaken for tuberculosis. Many of the cases he describes are instances of bronchitis or of localized infiltrations, often in the upper lobes, which disappear after a number of weeks. However, two or three of the cases pursued a chronic course and in their general clinical features closely resemble the cases Doctor Wolman and I have reported. In 1913 Riesman described a chronic form of pseudolobar bronchopneumonia with mild constitutional symptoms occurring in children and young adults. Months of delay in resolution often were a cause of great anxiety, but the fact that in the end the lesions did resolve

and the patients completely recovered seemed to us to distinguish this condition from the one that we described. Moreover in our cases there was none with a clear history of the symptoms having followed a definite attack of pneumonia.

A year after the publication of our article, in 1917, Garvin, Lyall and Morita reported nine cases of chronic nontuberculous lung infection which had been under observation for four years or longer. All had at first been diagnosed as pulmonary tuberculosis and only after prolonged observation had the nontuberculous nature of the infection been firmly established. The general clinical features of their cases were the same as of those we had described. Later in the same year, Miller published a comprehensive article in which he groups together the subacute form of bronchopneumonia described by Riesman, the subacute form of bronchopneumonia with recurrences, and the chronic form of basal infections, as varying clinical manifestations of the same underlying disease. I am not convinced that this grouping is justified but am willing to join together the recurring form of bronchopneumonia and the chronic basal lesions. In 1931 Austrian wrote a detailed review of the clinical manifestations of what he calls Chronic Basic Nontuberculous Disease of the Lungs and in the same year Krause published two articles emphasizing especially the clinical features of this condition in children.

The disease is not uncommon, the clinical course of events is characteristic and distinctive, and so I am convinced that every physician has observed it in his practice and that it is a familiar condition to those especially interested in pulmonary disease. Nevertheless, I shall refresh your memories with an account of the salient clinical features.

The disease occurs especially in children and during early adult life. In my own experience most cases come under observation between twenty and forty years of age. However, I am called upon to examine few children and judging from the reports of pediatricians the condition occurs frequently in early life. Indeed there are many observations which suggest that often the condition begins in childhood but the symptoms do not become pronounced until years later. When the disease is observed after fifty there is usually a long history of cough over many preceding years. Cough and expectoration, the chief symptoms, may have come on insidiously, or may have followed a cold, an attack of grip or may have developed in sequence to a more conspicuous pulmonary infection diagnosed as pneumonia. In children the symptoms often follow the pulmonary complications of one of the specific infections.

Once the symptoms have begun they may continue uninterruptedly, varying in intensity from time to time but never disappearing entirely. Or they may persist for months, then pass away, then, after a slight cold, return again, and so on at intervals for years. Gradually the periods of freedom from symptoms may become shorter, and finally cough and expectoration always may be present. Sometimes, in children and young adults, recurring attacks of atypical pneumonia come on, that is, pneumonia with signs of imperfect consolidation which persist for weeks or months before they clear, and mild constitutional reactions, each successive attack of pneumonia recurring at the same location.

The *constitutional symptoms* which accompany the continuous and recurring forms of chronic lower lobe infections are relatively mild and in this respect contrast glaringly with those of pulmonary tuberculosis. Nearly all the patients have fever, but usually a low fever, the afternoon temperature seldom exceeding 100°F. The fever may persist indefinitely at this level, year after year, or it may come and go with variation in the degree of cough and expectoration. One patient whom we observed almost continuously over a period of eight years had constantly during this time such a low fever, and even nine months spent at absolute rest in bed failed to reduce it. Nevertheless in spite of this persisting fever the patients maintain a good state of bodily nutrition and seldom lose weight. Nor do they often complain of loss of energy and strength or increasing fatigue.

Cough and expectoration are the outstanding symptoms of these chronic pulmonary infections. Usually the cough is especially pronounced in the morning, but it occurs throughout the day and not in brief, sharply defined paroxysms. In other respects there is nothing peculiar about the cough. It varies in intensity and character in different patients and in the same patient at different times. It may be a loose cough, always productive of sputum, or a more or less harrassing cough, which succeeds in raising only a small amount of tenacious expectoration. The one important feature of the cough is its variability; at one time, frequent and distressing, at another, almost negligible, at still another, perhaps entirely absent. The amount and character of the sputum is equally variable; it may be scanty, tenacious, mucoid, with relatively few cells, or it may be abundant and frankly mucopurulent. It never comes up periodically in mouthfuls as it does in frank bronchiectasis.

The bacteria present in the sputum have been carefully studied by many observers. No particular organism can be isolated regularly. The

pneumococcus, the influenza bacillus and various types of the streptococcus are the organisms usually obtained. Occasionally one organism may grow in pure culture, but more often two or three appear, although one form usually predominates. In the same patient the predominant organism may change from time to time; during one exacerbation it may be the pneumococcus, during another the influenza bacillus.

Haemoptysis is a very common symptom. Nearly all the patients have blood-streaked sputum and many of them raise small or large amounts of blood, from an ounce or two to a pint or more. In a few patients recurring large haemoptyses constitute the most striking and distressing feature of the disease. Such a large haemoptysis may come on unexpectedly at a time when other symptoms are slight or absent.

The physical signs have certain distinctive characteristics, namely, they are always located in one or both lower lobes, and they always remain permanently in the one location or if they come and go they always recur at the same location. I have the impression that the left lower lobe is involved much more frequently than the right. I wish there were evidence that would permit me to state this impression as a fact since it would have an important bearing upon a relation I shall discuss later. Usually there is a little dulness over the affected lobe and the breath sounds may be a little roughened or somewhat diminished in intensity but the characteristic and constant sign is the presence of localized moist râles. The râles may be scanty or profuse, they may be abundant at one time, absent at another. When these variations occur they usually, but not always, correspond with variations in the degree of cough and the amount of expectoration.

The ordinary roentgenogram is often disappointing since in view of the pronounced and constant physical signs it may show only slight or even negligible alterations. However, generally there is increased density of the usual pulmonary markings going to the affected lobe. No definite areas of pulmonary infiltration are revealed. Sometimes the diffuse clouding of pleurisy or the distortions caused by pleural adhesions are seen.

Sinus infections, often severe and wide-spread, almost regularly accompany chronic nontuberculous pulmonary infections. This is a universal finding commented upon by every observer who has written about this condition. In some series of cases as large a proportion as 80 per cent have been found to harbor sinus infections. Needless to say the relation between the sinus infection and the lung infection has been fully dis-

cussed. Some believe that the sinus infection is the direct cause of the inception and the future progress of the pulmonary disease; others that the two foci of infection occur together but bear no aetiological relation one to the other, both being the result of the same infection; still others that the pulmonary infection comes first and the sinus infection later as a result of continuous contact with infected material coming from the lungs. I am familiar with no observations which will permit us to come to an established conclusion about these differences of opinion. However, in my experience treatment of the sinus infection has no beneficial effect upon the chronic pulmonary disease. Nevertheless it is possible that treatment of the sinus infection at an early stage might prevent the onset of the pulmonary infection; and even had the pulmonary infection already begun it might perhaps prevent it from becoming firmly established as an ineradicable chronic infection.

How long these chronic basal infections may last I cannot say precisely. There are no studies of groups of cases followed from the beginning of the illness to the death of the patient and finally investigated at autopsy. However many observers have followed the course of events for ten years or longer and over this period of time the condition has not altered, certainly it has not disappeared. Therefore it is likely that when it has once become firmly established it will persist during the remainder of a life time. A certain number of the patients later develop the outspoken symptoms of bronchiectasis. I can find no records of postmortem studies of the lungs, which is not remarkable since sufferers do not die of the disease. The only autopsy I have witnessed or of which I have seen a report was performed upon a patient we had carefully watched over a period of six years. This patient was a white woman, forty years of age, who came to the Out-Patient Department of the Johns Hopkins Hospital in October, 1908, complaining of cough and expectoration which had come on insidiously a year and a half before. On one occasion she had had haemoptysis of moderate amount. The examination revealed a little dulness over the left lower lobe and numerous moist râles over this lobe and a smaller number of moist râles over the right lower lobe. No change occurred in the symptoms nor in the physical signs during a period of six years. Now and again she had small haemoptyses. Repeated sputum cultures yielded pure growths of pneumococcus. In August, 1914 she was taken acutely ill with pain in the right side and high fever. When admitted to the hospital ward a day or two later she presented the characteristic signs of a right pleural

effusion which upon aspiration proved to be purulent. She was desperately ill and died within twenty-four hours of entering the hospital, three days after the onset of the acute symptoms. Autopsy revealed an encapsulated pneumococcus empyema. In both lower lobes the bronchi were dilated, filled with purulent material, and about the dilated bronchi were scattered areas of bronchopneumonia.

During these many years it has been interesting to speculate upon the nature of the underlying pulmonary lesions which cause these characteristic symptoms of long duration. Certainly chronic nontuberculous basal infection of the lungs is not a specific disease caused by the activity of a certain organism. From the beginning of our studies it has been demonstrated again and again by many observers that the infecting bacterium is a different one in different patients and that in the same patient the predominant organisms may change in successive exacerbations of the disease. Therefore it has seemed to be clear that the essential cause of the symptoms must be some underlying alteration in the structure of the lung which facilitates infection and provides a sheltered harbor where bacteria once introduced may prosper and multiply. There is some direct and much circumstantial evidence to convince us that the underlying alteration consists of changes in the walls of the smaller bronchi and in their lumina; in a word, that these chronic basal infections are a form of bronchiectasis. However, if we are to speak straightway of the conditions I have described as bronchiectasis, then we must very radically change our clinical definition of bronchiectasis, because until at least very recently the term has been used to designate a characteristic group of symptoms entirely different from those presented by the patients I have been describing. Nevertheless this difficulty need not deter us, for all that is necessary is that we enlarge our concept of what bronchiectasis really is and begin to include under this heading early stages and mild forms of the disorder and not reserve it only for late and advanced stages. Until recently the diagnosis of bronchiectasis was difficult and could be made confidently only when the characteristic symptoms were pronounced. It is illuminating to read what Hoover wrote in an article upon diseases of the bronchi published in 1920 in the Oxford System of Medicine: "The writer has never had the opportunity to prove bronchiectasis on any other than inferential grounds." The very next year, 1921, Sicard and Forestier introduced bronchography and this beautiful method of outlining the bronchial tree has completely changed our clinical views about bronchiectasis. We now regard it as a common

disease with a varied symptomatology, the advanced typical forms of the disease constituting only a small proportion of the cases.

If now we return to consider the symptoms of chronic nontuberculous basal lesions and look upon them as the possible manifestations of bronchiectasis we shall find abundant support for this point of view. The frequent onset in childhood, the common history of chronic cough beginning after an acute respiratory infection, the long duration of the illness with only slight constitutional symptoms, the variations in the intensity of the symptoms, the tendency to recurring haemoptysis, the character and strict localization of the physical signs, the absence of evidence of pulmonary infiltration in the roentgenogram, all of these manifestations are closely analogous to those of bronchiectasis. To this we may add the facts that a considerable proportion of the cases finally develop the symptoms of advanced bronchiectasis and that an occasional autopsy has demonstrated the presence of bronchiectasis.

We would think that bronchography had long ago settled this question by demonstrating bronchial dilatation in the affected patients. So it has in isolated instances of the disease, but not in sufficiently large groups to demonstrate in which patients with chronic cough there is bronchial dilatation, in which there is no dilation, and to correlate these differences with differences in the clinical manifestations. Until recently bronchography has not had a wide application and there are many details about the behavior of the bronchi in health and in disease that require further elucidation. I am quite sure there is not yet a uniform opinion among roentgenologists as to the exact criteria for the diagnosis of early or beginning bronchiectasis. Apparently under certain circumstances the bronchi or the bronchioli may dilate and subsequently return to normal. For instance, Ochsner studied a large group of students with chronic cough, often without expectoration, and found bronchial dilatation in about 90 per cent. Following treatment the cough disappeared and a second bronchogram taken at that time unexpectedly demonstrated that the bronchial dilatation had also gone. Likewise Christopherson, on the basis of over two hundred examinations, concludes that in only a small number of patients with chronic cough do we fail to find some evidence of alteration in the calibre of the bronchial tubes. The usual picture is a varicose, beaded or fusiform appearance of the bronchial tree, most pronounced as a rule in the larger tubes. Apparently Christopherson also considers these changes reversible, since he regards them as being due to alteration in the autonomic nervous system leading to

relaxation of the bronchial musculature. Cherry examined a number of patients with chronic cough dividing them into two groups; the first, comprising 62 per cent of the patients, showed definite bronchial widening in the bronchogram, the second, comprising 38 per cent, showed no widening. Patients in the first group nearly all had the signs of basal lesions, patients in the second group had no abnormal physical signs. Cherry regards the bronchial widening as due to some developmental error, those unfortunate enough to have widened bronchi being predisposed to develop basal bronchitis and bronchiectasis, whereas those with normal bronchi never develop bronchiectasis. Wilson reports his observations upon eight patients with chronic cough, five with persistent basal râles, three without any abnormal chest signs. In all of the five cases with lower lobe râles the bronchogram demonstrated enlargement of smaller bronchi in the location where the râles were heard; in the three without chest signs the bronchial tree was normal. Therefore what evidence we have from bronchographic examinations certainly confirms the impression that bronchiectasis is the underlying anatomical lesion of chronic nontuberculous basal infections. However, our knowledge of the details of bronchial configuration is not so complete as we should wish it to be and we can only say that it is likely that all cases of chronic basal infections would show bronchiectasis were they carefully studied, but we cannot predict this result with confidence.

When chronic basal infections have been present for years there is no treatment that will cure them. If the underlying lesion is bronchiectasis we cannot expect the bronchi to resume their normal contour and function. Even though only the smaller bronchi are dilated these pockets form favorable sites for infection to settle and to persist. Fortunately the condition does not threaten life and in most instances does not prevent the patient from following the usual routine of living. Therefore the problem of treatment is to alleviate symptoms which are an annoyance and a handicap. What may be gained by treating the upper respiratory infections, almost always present, I cannot say. In my own experience the results have been disappointing, but apparently others have fared better because most authors firmly insist that these infections when active may constantly reinfect bronchiectatic cavities and thus prevent other methods of treatment from operating successfully. Moreover the presence of a severe sinusitis alone may have an undermining effect upon the general health. Therefore I would not neglect to give upper respiratory infections appropriate attention, although I should not

enthusiastically anticipate that the pulmonary symptoms thereby would be greatly improved.

Vaccines are useless. We gave vaccines a very thorough trial and I have never seen the slightest benefit from their use. All observers who have used them agree with this conclusion.

There is difference of opinion about the value of injecting lipiodol into the affected bronchi. Some report striking improvement after the injections, others that no improvement results. No definite statement can yet be made about the value of this method of treatment.

Postural drainage systematically and faithfully carried out is often beneficial. Garvin and his coworkers enthusiastically recommend this procedure.

Phrenicectomy has been proposed but I have never seen this operation performed on a patient with chronic basal infection. From what I know of the results in patients with pronounced bronchiectasis I should be surprised were it to prove helpful.

Recently reports have appeared lauding the beneficial results of the roentgen ray treatment of these chronic lung infections. I have had no experience with this method of treatment and therefore cannot express an opinion about its value.

Climate has been vaunted as a very helpful factor in treatment. Krause especially has recommended it enthusiastically. I have no doubt that in many cases it will prove to be advantageous especially in those with long periods of freedom from symptoms. A characteristic of chronic basal infections is that the symptoms are always aggravated or started afresh by colds and other mild respiratory infections. To get away from the crowded city and the inclemency of the North and spend the winter out of doors in Arizona will certainly benefit the symptoms and perhaps even temporarily abolish them. That a long residence in a suitable climate will eventually bring about a cure I consider very unlikely.

The treatment of chronic basal infections is necessarily palliative and unsatisfactory. Perhaps something more could be accomplished by directing our efforts toward prevention. I have expressed the opinion that many cases of chronic basal infection have their inception in childhood even though they may seem to arise later in life. Therefore we may consider especially the conditions that exist among children. At that early age respiratory infections are very prevalent and are often followed by weeks and months of coughing, no doubt correctly attributed to a persisting bronchitis. Long continued bronchitis seems to follow

particularly that form of pneumonia spoken of as interstitial, which is a frequent complication of the specific infections of childhood. Children may cough winter and summer for years or they may cough only during the winter months. When the cough is still more periodic they are said to be susceptible to colds. Out of this large group of children with cough, most finally recover and when they are ten or twelve years of age "outgrow" the tendency to take cold and later in life show no evidence of impairment of the respiratory apparatus. Only a small number acquire manifest bronchiectasis or chronic basal infections which are, as I have pointed out, mild forms of bronchiectasis due to dilatation of the smaller bronchi. Until these serious and permanent alterations have become established there is no possible way of discovering which children with chronic or recurring cough will at last fully recover, which will be left with more or less distortion of the bronchi. Therefore, if prevention is to accomplish anything, it must consist of solicitous care of all children with acute respiratory infections and particularly of those with persisting cough.

In the first place convalescence from acute respiratory infections should be more seriously regarded than is the prevalent custom, and children not allowed out of bed until cough has completely disappeared. The ordinary mild cold followed by bronchitis should not be neglected. Safeguards must be thrown about those with chronic or recurring colds; they must be protected from infection, from fatigue and from unnecessary exposure.

It is an almost universal custom to remove the tonsils and adenoids of children with chronic or frequently recurring cough. This seems to be prudent foresight since even though it may serve no other useful purpose it does reduce the chance of infection of the ears. But what to do about infected sinuses is indeed a problem. Operative treatment, except conservative measures, does not improve the situation. At the present time roentgen ray treatment is being employed and many favorable reports have been published. Children with recurring winter cough are often greatly benefited by spending successive winters in a warm climate away from contact with those infected with colds. As their general health improves, frequently the sinus infection also subsides.

It is needless to point out how difficult it would be to furnish proof of the efficacy of such a plan of prevention. All we can say at the moment is that the plan is reasonable and that it seems to work beneficially in individual cases.

I have presented evidence which I think justifies the assumption that chronic basal infections of the lungs are forms of bronchiectasis. Therefore, in concluding, it is appropriate that I say a few words about the aetiology of bronchiectasis.

It is a matter of daily observation that of innumerable people who have respiratory infections of one sort or another only a small number are left with permanent changes which cause chronic cough and expectoration. Of those with chronic cough and expectoration only a few have localized basal lesions which mark the location of bronchiectatic dilatations. Therefore special conditions must develop which, under appropriate circumstances, lead to bronchial dilation. Many authors stress in this connection the importance of congenital faults in development. It is a view that has been widely discussed in medical literature but one that has found few warm adherents. Were it true, we would be obliged to concede that congenital anomalies of the bronchi occur with astonishing frequency and experience teaches us that they do not.

When we discover bronchiectasis at the postmortem table we always look carefully for evidence of obstruction to the bronchi because the origin of bronchiectasis can be satisfactorily explained only when bronchial stenosis is demonstrated. In those cases in which the bronchi are found to be patent the explanation for the bronchial dilatation is left to ingenious speculation. It would simplify matters greatly were we justified in assuming that all instances of bronchiectasis are due to bronchial stenosis even though the stenosis may have been transient and no trace of its former presence be found at autopsy. There is a growing body of evidence that lends support to this view.

In the development of bronchiectasis we must consider two factors: first, infection which weakens the walls of the bronchus; second, changes in pressure which tend to dilate the bronchus. The matter of infection has been thoroughly studied and we know all the details of the injury sustained by the bronchial wall. In contrast to this secure knowledge is the uncertainty of our speculation about the mechanical factors which increase intrabronchial pressure. Many have thought that merely the stagnation of infected material is sufficient to distend the bronchus; others that the stress of ordinary breathing will dilate a bronchus with very weak walls; still others that in some cases the pull of pleural and pulmonary scars accounts for the dilatation; still others emphasize especially the effects of cough. However, throughout these discussions,

which have been waged since the days of Laennec, many voices have been raised to insist upon the preëminent rôle of bronchial stenosis. Recently Andrus has considered anew the mechanics of respiration and comes to the conclusion that deep breathing, coughing and fibrosis do not raise intrabronchial pressure and therefore can play no part in the development of bronchiectasis. He contends that bronchial stenosis with lobar atelectasis is the only condition within the chest that can exert a dilating effect upon the bronchi. He insists that bronchial stenosis with atelectasis is a necessary condition for the development of bronchiectasis.

When a lobar bronchus is occluded the lobe supplied by the bronchus soon collapses. With the collapse of the lobe the pressure on that side of the chest is greatly reduced. Since the chest wall is rigid and cannot be retracted this fall of pressure is partly compensated for by elevation of the diaphragm and displacement of the mediastinum. However these adjustments serve only to equalize the pressure between the two sides of the chest; the lungs themselves must distend to fill the space left vacant by the collapsed lobe, and this distension greatly increases the elastic tension which is exerted throughout the lungs. The pull of this elastic tension may be estimated by measuring the pleural pressure, which often falls more than to -100 cm. of water. Andrus has calculated that the main stress of this pull will fall upon the collapsed lobe and in a direction favorable to dilating the enclosed bronchi.

The conclusions reached by Andrus agree in general with those of Hedblom and of Weinberg who contend that complete bronchial obstruction is the most important single factor in the production of bronchiectasis. At variance with these views are the experimental results published by Adams and Escudero. These observers find that in dogs bronchiectasis follows partial occlusion of the bronchus; in none of their experiments did bronchiectasis follow complete occlusion. Faced by these contradictory results we must await further evidence before we can decide whether it is complete or incomplete bronchial occlusion that produces bronchiectasis. It may be that under certain circumstances one will be the cause and under dissimilar circumstances the other. Perhaps the mechanism may vary in different animals. The very delicate, flexible mediastinum of the dog may make this animal an unsuitable one upon which to demonstrate the effects of the elastic tension which accompanies collapse of the lung in other species. Never-

theless, whatever may be the final decision about this detail of the mechanism, accumulating evidence points to bronchial obstruction, partial or complete, as an essential factor in the development of bronchiectasis.

From the clinical standpoint there are many considerations which lead us to believe that transient bronchial stenosis occurs frequently. Common causes of transient stenosis are plugs of viscid secretion within the bronchus and pressure of enlarged bronchial lymph nodes. I think the view is now almost universally held that atelectasis or pulmonary collapse is always due to bronchial occlusion, in acute cases usually to masses of tenacious secretion. It is likely that this form of bronchial stenosis occurs frequently in the course of respiratory infections especially in infants and children. I am much impressed by the rapidly growing number of observations published by pediatricians which demonstrate that pressure from enlarged mediastinal lymph nodes frequently produces the symptoms of bronchial stenosis. In the course of pulmonary infections the mediastinal nodes often swell and press upon the bronchi and plugs of tenacious secretion may readily lodge at these constricted areas and complete the occlusion of the bronchial lumen. If the bronchial walls are attenuated and greatly weakened by infection those in the collapsed lobe may quickly become distended and the dilatation persist after the bronchial obstruction has been overcome and the collapsed lobe has reëxpanded.

That this view is not entirely fanciful is suggested by the remarkable and well established fact that in children bronchiectasis occurs nearly three times more often in the left lower lobe than in the right. Certainly the left lower lobe is not more frequently the seat of infection than the right lower lobe and we would surmise that there is some peculiarity about the structure, position, and course of the left lower bronchus to account for the striking difference in the occurrence of bronchiectasis in the two lower lobes. In this relation the following facts are pertinent: (*1*) The right main bronchus is almost a direct continuation of the trachea whereas the left branches off at a sharp angle. (*2*) The left main bronchus is much narrower than the right. (*3*) There is a definite constriction of the left bronchus at a point just before the bronchus to the upper lobe is given off. It is at this point that the left pulmonary artery crosses the bronchus. These differences between the two main bronchi would certainly make it easier for the left bronchus to be occluded either by a plug from within or pressure from without.

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LARYNGEAL CHANGES IN ACUTE HAEMATOGENOUS TUBERCULOSIS[1]

WILLIAM H. OATWAY, JR.

Pulmonary tuberculosis, miliary tuberculosis and laryngeal tuberculosis are at times unrecognized even in advanced stages. The result of this failure is a sad clinical condition and an unfortunate public health problem. Any warning which might mitigate these circumstances would be decidedly helpful.

During the past three and one-half years a peculiar, florid, symptomatic type of laryngitis has been seen in a considerable number of cases. It has almost invariably occurred in cases of chronic pulmonary tuberculosis with an acute haematogenous dissemination. Its presence has not only been an indication of tuberculous disease and a particular type of lesion, but has been directly correlated with infectiousness and other clinical findings, and it has been a deadly prognostic sign.

CLINICAL DESCRIPTION

The lesion has usually involved the laryngeal structures, the epiglottis, the pharynx and the palatine arch. The chief sign has been a gross swelling, usually accompanied by injection, often by necrosis and ulceration, and occasionally by miliary spots at the periphery of the major area. Characteristically the cords could not be seen by indirect laryngoscopy; the arytenoids were grossly swollen and injected, though occasionally gelatinous; the epiglottis was similarly swollen and turban-shaped; the pharyngeal and palatine structures were somewhat swollen but almost routinely necrotic and sloughing. At times the larynx was necrotic; the swellings limited by an intrinsic network of fibrosis; or the oral structures (gums, tongue and buccal membranes) were involved.

The symptoms were usually those of an endogenous laryngeal involvement. Hoarseness and aphonia were usually present, but pain and dysphagia were invariably severe and progressive. Food and fluid intake

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was difficult and agonizing; insufflation a common result; and analgesics were only partly effective.

ORIGIN OF DATA

A description of the patient material in the Wisconsin General Hospital is pertinent to the data. The average daily census of the hospital during the period under discussion (three and one-half years) has been 660, and a total of 39,752 patients has been admitted. Some of the patients come from cities and towns but many of them are of rural origin. Eighty-six per cent were state cases (financed by state-county funds), 8 per cent were clinic patients (paying a moderate basic rate for all services), and 6 per cent were private. The state and clinic patients are allocated to the most suitable service by a medical admitting officer. There has been no routine admission test for tuberculosis (except for a three-month period in 1935) (24) but information from the home physician and the use of a fluoroscope have been available to the admission service. The clinical examination of the patients on the ward is usually thorough, since it is a teaching hospital.

The numbers of admitted patients, cases of pulmonary tuberculosis, miliary tuberculosis and laryngeal tuberculosis, are listed below. The author has examined more than three-quarters of the cases of pulmonary and miliary tuberculosis, and all of the cases of laryngeal disease reported.

Hospital admissions—three and one-half years	39,752
Cases of pulmonary tuberculosis	720
Per cent of admissions	1.8
Cases of miliary tuberculosis	25
Cases of possible miliary tuberculosis	8
Per cent of admissions	0.08
Cases of laryngeal tuberculosis	101
Per cent of admissions	0.25
Per cent of pulmonary tuberculosis	14.0
Cases with chronic laryngeal lesion	81
Cases with acute laryngeal lesion	20

The incidence of chronic and acute tuberculous laryngitis in cases of pure or combined miliary and parenchymal disease is noted below. The frequent occurrence of an acute laryngitis in cases with definite or possible miliary plus parenchymal disease is obvious.

Cases of chronic tuberculosis of larynx	80
With miliary tuberculosis, no chronic lung lesion	0
With miliary tuberculosis, plus chronic lung lesion	0
With possible miliary tuberculosis, plus chronic lung lesion	0
With chronic lung lesion, no miliary tuberculosis	80

Cases of acute tuberculosis of larynx	20
With miliary tuberculosis, no chronic lung lesion	1
With miliary tuberculosis, plus chronic lung lesion	11
With possible miliary tuberculosis, plus chronic lung lesion	8
With chronic lung lesion, no miliary tuberculosis	0

PRESENTATION OF CASES

A description of the cases and a demonstration of their importantly similar diagnostic points can best be given briefly in tabular form.

The cases have been subdivided into two groups. In the first group (table 1) there are 10 cases, all of which had an acute tuberculous laryngitis, a chronic tuberculous lung lesion and an acute miliary tuberculosis. In the second group (table 2) there are 9 cases, all of which had an acute laryngitis. Eight of these had a chronic lung lesion, but a miliary disease which was indefinite; the ninth case had a miliary disease but the lung lesion was limited to multiple calcifications of an old nodal-parenchymal lesion.

The abnormal extent of the leucocyte count, the sedimentation rate and the laryngeal symptoms have been represented by an estimation which ranges from 0 to 4+. This is a crude but simple and effective scale. The pathological signs which were present in the throat structures are noted according to numbers, which are interpreted at the bottom of the tables.

ANALYSIS OF DATA

Examination of the data presented in tables 1 and 2 has developed many interesting points.

1. Chronic tuberculous laryngitis (low-grade, intrinsic) was found exclusively in association with pulmonary tuberculosis. Acute tuberculous laryngitis (florid, extrinsic) occurred exclusively in miliary, or possible miliary, disease superimposed on a chronic pulmonary tuberculosis. Almost all cases of combined miliary and parenchymal disease developed an acute exudative laryngitis.

2. The sex incidence was predominatly male (16 of 19 cases).

3. The age-group was definitely late (13 patients were over forty years; the average age was 45.5).

4. The associated pulmonary tuberculosis was usually chronic (5.8 years average in 16 cases); it was often undiagnosed (12 of 18 cases); and had usually existed without definite treatment (9 of 18 cases had no rest, 12 had never had sanatorium care, 17 had no isolation nor care immediately previous to hospital diagnosis).

TABLE 1

NAME	1 H.A.S.	2 K.L.	3 K.O.	4 W.R.	5 L.A.M.	6 M.O.N.	7 M.Y.	8 B.O.	9 P.F.	10 K.E.
Sex	M	M	M	M	M	F	M	M	M	M
Age	42	24	23	62	52	28	49	47	48	49
Service	ENT	Thoracic	ENT	ENT	Surgical	Thoracic	Thoracic	Medical	Thoracic	Medical
Pulmonary tuberculosis	+	+	+	+	+	+	+	+	+	+
Previous diagnosis	+	0	0	0	0	0	0	+	+	0
Duration of symptoms	17 years	3 months	2–6 years	?	4 years	3 years	?	10 years	5 years	6 months
Previous therapy	2 years	0	0	0	0	2 months	0	1 year	4 years	6 weeks
X-ray of lungs:										
Chronic tuberculous lesion	+	+	+	+	+	+	+	+	+	+
Cavitation	+	+	0	+	+	+	+	+	0	+
Emphysema	0	+	0	+	0	0	+	+	0	+
Miliary lesion	+	+	+	+	+	+	+	+	+	+
Clinical data:										
Sputum for tubercle bacilli	+	+	+	+	+	+	+	+	+	+
Fever	2°	3°	2°	3°	3°	3°	3°	2°	3°	2°
White blood cell count	3+	3+	3+	4+	4+	2+	4+	3+	2+	3+
Sedimentation rate		3+		3+		3+			3+	3+
Laryingeal tuberculosis	+	+	+	+	+	+	+	+	+	+
Previous symptoms	?	0	3½ months	0	4 years	5 months	?	0	10 months	0
Previous therapy	0	Local	Coagulation	Exodontal	Local	Transfusion	Local	Local	Sedative	0
Acute duration	6 weeks	6 weeks	4 weeks	3 weeks	6 weeks	4 months	3 months	4 months	5 weeks	?
Symptoms:										
Aphonia	2+	3+	3+	1+	1+	2+	2+	3+	2+	2+
Dysphagia	3+	3+	3+	3+	4+	2+	3+	2+	4+	0-2+
Pain	3+	3+	3+	3+	3+	2+	3+	2+	4+	0-2+
Signs in throat*:										
Larynx	?	1,2	?	?	1,2,3,4	?	?	1,2,3,4	1,2,6	1
Epiglottis	1,2	1,2,3	1,2,3	1,2,3	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,6	1
Pharynx	1,2,3	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3	1,2,3,4	1,2,3,4,6	1
Palate	1,2,3,4	1,2,3,4,5	1,2,3,4	1,2,3,4,5	1	1,2,3,4	1	?	1,2,3,4,5,6	1
Fate of patient:	Died	Died	Died	Died	Died	Died	Died	Died	Died	Died
Interval after diagnosis	2 weeks	3 weeks	4 weeks	6 weeks	2 weeks	4 weeks	4 weeks	4 weeks	12 weeks	4 weeks
Total acute illness	8 weeks	9 weeks	8 weeks	10 weeks	8 weeks	20 weeks	16 weeks	20 weeks	18 weeks	9 weeks

* 1, injection; 2, oedema; 3, necrosis; 4, ulceration; 5, miliary areas; 6, granules.

TABLE 2

	1	2	3	4	5	6	7	8	9
NAME	G. A.	O. A.	H. A. C.	B. E.	I. M.	L. A. R.	M. A.	J. U.	M. O. R.
Sex	M	M	M	M	M	M	M	F	F
Age	38	68	43	54	46	34	60	23	69
Service	Medical	ENT	Thoracic	ENT	Medical	Thoracic	ENT	Thoracic	Medical
Pulmonary tuberculosis	+	+	+	+	+	+	+	+	0
Previous diagnosis	0	0	0	0	+	+	0	+	0
Duration of symptoms	13 months	2 years	14 years	10 months	11 years	10 years	2 years	8 years	0
Previous therapy	0	4 months	0	0	1 year	2 years	0	2 years	0
X-ray of lungs:									
Chronic tuberculous lesion	+	+	+	+	+	+	+	+	0 Ghon
Cavitation	+	+	+	+	+	+	+	+	0
Emphysema	+	+	+	0	+	+	+	+	0
Miliary lesion	?	?	?	?	?	?	?	?	+
Clinical data:									
Sputum for tubercle bacilli	+	0	+	+	+ gastric	+	+concentration	+	+
Fever	3°	0	4°	3°	3°	3°	4°	3°	0
White blood cell count	2+	4+	3+	4+	3+	4+	3+	3+	N
Sedimentation rate	2+		4+		3+	4+	3+	2+	3+
Laryngeal tuberculosis	+	+	+	+	+	+	+	+	+
Previous symptoms	0	8 months	Few years	0	?	Few years	4 months	5 months	0
Previous therapy	Local	For carcinoma	0	For carcinoma	Local	Opiate	0	Silence	U-V
Acute duration	3 months	5 months	6 weeks	2 months	1 month	3 months	8 weeks	5 weeks	7 weeks
Symptoms:									
Aphonia	2+	2+	1+	2+	1+	4+	2+	2+	2+
Dysphagia	3+	3+	3+	3+	2+	3+	3+	2+	1–3+
Pain	3+	3+	3+	3+	3+	3+	3+	3+	3+
Signs in throat*:									
Larynx	1, 2, 4	1, 2, 4	1, 2, 6	2, 3	1, 2, 3, 6	1, 3, 4	1, 2, 3, 4	2, 3, 4	2, 6
Epiglottis	1, 2, 3, 4	1, 2, 4	1, 2, 6	2, 3	1, 2, 3, 4, 6	1, 3, 4	1, 2, 3, 4	1, 2, 3, 4	2, 6
Pharynx	1, 2	1, 2, 3, 4	1, 2, 6	2, 3	1, 2, 3, 6	1, 3, 4, 6	1, 2	1, 2, 3, 4	1, 3, 4, 5
Palate		?					1		1, 3, 4, 5
Oral	+		+					+	
Fate of patient	Died	Died	Died	Died	Died	Died	Died	Ill	Died
Interval after diagnosis	8 weeks	8 weeks	5 weeks	20 weeks	6 weeks	10 days	28 weeks	18 months	12 weeks
Total acute illness	22 weeks	28 weeks	12 weeks	28 weeks	10 weeks	16 weeks	36 weeks	23 months	18 weeks

* 1, injection; 2, oedema; 3, necrosis; 4, ulceration; 5, miliary areas; 6, granules.

5. The acute laryngeal lesions had been preceded by symptoms of chronic laryngitis in about half of the cases. The acute lesions were incorrectly diagnosed in almost every case, and had been treated in a variety of ways for several different conditions, most frequently carcinoma.

6. The onset of the acute laryngitis coincided with a sudden change in the patient's general health. The duration of the lesion and general change varied from three to twenty weeks, with an average of eight and a half weeks.

7. Twelve of the patients were admitted to other services than the Thoracic Service, thus adding an exposure of hospital personnel to the exposure of home contacts.

8. The lung lesion was usually advanced enough to be cavitated (16 of 18 cases). The sputum was positive in all but one case.

9. A compensatory emphysema was present, in addition to the gross parenchymal lesion, in 12 of the cases. This made the diagnosis of miliary tuberculosis very difficult by X-ray. (Seven of the 9 cases in which miliary tuberculosis could not be certainly diagnosed had emphysematous lungs.)

10. Most of the cases were markedly febrile, had a "septic" blood count of considerable degree, and (when taken) a rapid sedimentation rate.

11. Symptoms of the acute laryngitis were the ones usually found in a deep involvement of the extrinsic laryngeal structures. Pain and dysphagia were slightly more prominent than hoarseness and aphonia.

12. The most prominent sign of the acute laryngitis was a gross swelling. Injection, necrosis, ulceration and granulation were usually seen, in that order of frequency. In a few cases miliary spots in the mucosa were seen in the periphery of the lesion.

The extrinsic (perilaryngeal) structures were almost invariably involved. This included the epiglottis, pharyngeal walls, tonsils, pillars and uvula. Several cases had lesions in the mouth, and in one the chief site of a nodular disease was the tongue. The distribution was usually symmetrical. Where asymmetry was observed it seemed to be caused by old cicatrization.

13. The progress of all of the patients has been followed.

(a) All 10 patients with definite miliary disease are dead (table 1). The duration of life after diagnosis varied from two to twelve weeks, with an average time of four and a half weeks. The average total duration of the acute illness was twelve and a half weeks.

• 1, injection; 2, oedema; 3, necrosis; 4, ulceration; 5, miliary areas; 6, granules.

(b) Eight of the 9 patients with indefinite miliary disease are dead, with a range of ten days to twenty-eight weeks or an average time of eleven weeks after diagnosis, and an average total duration of the acute illness of twenty-one weeks.

(c) The average survival time is lower for those cases which could be definitely diagnosed by X-ray as miliary disease.

14. Necropsies were possible on very few patients, since they were transferred to sanatoria soon after diagnosis.

(a) Two of the "definite" miliary cases were examined: one had an acute generalized miliary tuberculosis; the other had a generalized acute and old haematogenous (protracted) dissemination. Two others of this group had biopsies taken: one showed miliary tuberculosis of the tongue; the other showed miliary tubercles of the tonsil.

(b) One of the "indefinite miliary" group was examined and was found to have the lesion of a generalized protracted dissemination.

15. It is difficult to present a complete picture of the throat lesions. They have been hard to visualize completely; one tends to omit parts of a description even when a special effort has been made; and photography has been impossible.

DISCUSSION OF THE SYNDROME

The literature is almost barren of important references to laryngeal changes in miliary tuberculosis except for a few recent publications. Most of the textbooks have added little in recent years to the earlier conceptions, as shown by a survey of two dozen volumes published between 1872 and 1937. Haematogenous infection of the larynx has been called a theoretical possibility by some, a rarity by most authors. Involvement of the larynx in miliary disease is also said to be rare. Some texts describe the laryngeal lesions as a miliary nodulation followed by ulceration, but most recently remark on the congestion and oedema as well. One authority says that the pathological process is the same whether primary or secondary. Tuberculosis of the larynx and pharynx is said by several to be sudden in onset and fatal in outcome. Pain is said to be due to infiltration of the arytenoids and epiglottis, dysphagia to infiltration of the epiglottis and aryepiglottic folds. Bosworth mentioned the turban-shaped epiglottis in 1892 (3).

Articles in the recent literature by Menzel, McMahon, and Myerson have given the subject more detailed and accurate consideration. Men-

zel (19), from Germany, in 1935 reported a study of the laryngeal lesions in 72 cases of haematogenous pulmonary tuberculosis. Men were more frequently affected than women; the structures at the entrance to the larynx were often involved; the prognosis was less favorable if the lesions spread to the pharynx; the course was variably chronic or acute; about two-thirds of the cases were fatal; the local developments depended upon the state of the general infection, which at times became improved.

McMahon (18) described the modern conceptions of pathogenesis and symptoms very well in 1937. He noted the involvement of extrinsic laryngeal structures in a symmetrical manner by haematogenous disseminations. The lung lesions were said to be usually focal deposits in the upper two-thirds of the fields. Symmetrical, extrinsic lesions accompanying a haematogenous spread could be superimposed on the earlier asymmetrical, intrinsic lesions present in pulmonary tuberculosis.

Myerson (21) analyzed a large series of tuberculous larynges in 1939. He credits Isambert with first describing the acute lesions in France in 1875. Myerson believes that haematogenous inrection is a more important portal than generally credited, and described the case of a male with an acute, diffusely hyperaemic larynx and pharynx secondary to a miliary spread. He considers that the pathological process represents an invasion of the larynx by large numbers of bacilli from the bloodstream. It may follow tonsillectomy or occur in advanced, severely sick patients. In the acute form the progress was rapid and fatal, with the hyperaemic, granular lesions seen best in the pharynx, becoming necrotic and deeply ulcerated. The benign form had fewer nodules, in only one or two structures, in a less uniform and fused distribution. The progress was slower and the process occasionally healed. It was painless and often left scars. He did not discuss the associated pulmonary lesions.

It would seem from our observations that the condition is not remarkably rare and that it might be a considerable social and public health problem. Reasons for the inability to diagnose miliary lesions have been mentioned earlier (extensive parenchymal lesions; compensatory emphysema). Other reasons have been found in the literature: lung lesions in haematogenous spreads are often found only in the upper two-thirds of the lungs (18) and half of the patients with miliary tuberculosis at necropsy had no lung lesions according to X-ray, with many lesions not visible until late (28). The tendency of patients with advanced laryn-

geal disease to produce apparent haematogenous lesions by aspiration of liquid pharyngeal contents into the bronchioles has also been mentioned by Amberson.

The differences in the appearance of lesions and the rate of progress would seem to be due to the balance between the host and the parasite (25). In some cases the dose is small or well resisted, and may be recurrent ("protracted haematogenous dissemination") (7, 20); in others the dose is large or poorly resisted and produces an acute generalized haematogenous tuberculosis. The fate of the laryngeal lesion varies with the systemic disease. Our cases would seem to lend strength to these points.

The cause for the constant presence of acute swelling may be a local hypersensitiveness due to previous involvement of the larynx. In all of our cases the miliary tuberculosis was a superinfection, and in all patients but one was superimposed upon advanced and infectious disease. Probably others than those so listed had previously had a chronic contact infection of the larynx, since many such cases are silent or undiagnosed. Although only 11.6 to 20 per cent of tuberculous patients are found to have lesions of the larynx, 75 per cent or more of terminal far advanced cases have been found involved. There seems to be no apparent reason for the dominant occurrence in males. The incidence of chronic laryngeal tuberculosis is said to be about the same for males and females.

Involvement of oral structures also occurs more frequently in males, but no certain evidence of haematogenous origin has been presented in such reports, and the progress of such cases has been different (6, 16, 26).

CONCLUSIONS

An acute oedematous laryngitis and pharyngitis with a progressively destructive tendency and severe symptoms of pain, dysphagia and hoarseness has been seen in 19 instances.

It occurred predominantly in males and often in a relatively advanced age group.

There had been a definite, or possible, haematogenous dissemination in all cases, as seen in X-ray films of the lungs, and there was almost invariably an underlying chronic, advanced and infectious pulmonary tuberculosis.

The syndrome has been rapidly fatal in all but one of the 19 cases.

The condition is not extremely rare.

The standard literature contains few references to its occurrence. The pulmonary and laryngeal tuberculosis was usually undiagnosed before admission to the hospital. The cases present a serious public health problem which can be minimized by recognition and isolation.

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THORACOSCOPY[1, 2]

A Conservative Measure in Artificial Pneumothorax

C. GERALD SCARBOROUGH

It is common belief to-day among physicians interested in tuberculosis that artificial pneumothorax, combined with some degree of bodily rest and a general restoration of physiological balance, is the treatment of choice for a large number of cases of pulmonary tuberculosis. This belief, however, hinges entirely on the important point of whether or not there is satisfactory collapse. After two or three months' trial, the physician should ask himself at least two pertinent questions about each pneumothorax:

1: Does it relax the infiltrated area of lung?
2: Does it close the cavity present?

A pneumothorax that fails of its primary objectives of relaxation of noncavernous lesions or of cavity closure must be considered a poor therapeutic measure. Therefore, a negative answer to either of the above questions should warrant a thorough investigation of methods to achieve the desired result—a relaxed lung. Pinner (1) states:

Pulmonary collapse, i.e., reduction of total pulmonary volume, always causes elastic relaxation, regardless of the method by which collapse is induced. Relaxation diminishes or eliminates elastic tension which counteracts the natural shrinking tendency of scar tissue; it abolishes the traumatizing effect of the continuous strain on tissue under high elastic tension; and it allows cavity walls to approximate, thus establishing the mechanical prerequisite for spontaneous healing processes. . . . Elastic relaxation produces conditions obviously favorable for healing and it is a constant factor in all forms of collapse therapy. It seems justified, therefore, to regard elastic relaxation as an important and probably the most important factor in enhancing healing under collapse therapy. It is therefore of greatest importance to assure it. In a pneumothorax, adhesions inserted over parenchymal lesions may com-

[1] From the Tuberculosis Division, Santa Clara County Hospital, San Jose, California.
[2] Presented before the Clinical Surgical Section of the California Tuberculosis Association, Santa Cruz, California, April 15, 1939.

pletely prevent elastic relaxation, and exert an elastic strain whose inspiratory and expiratory variations may be greater than before collapse.

Considered from this angle, an unsatisfactory pneumothorax is worse than none at all. The presence of restraining adhesions, therefore, is an obstacle which it becomes necessary to hurdle in order to offer the best possible treatment to the patient. It can be argued, as Cutler (2) does, that half-way measures, meaning incomplete collapses, accomplish the result in many cases. It is undoubtedly true that this does occur, but who is wise enough to predict which case will heal despite adhesions and which will not? Certainly a method that renders a precarious method of treatment of an unpredictable disease as fool-proof as possible is a worthy addition to our armamentarium.

Anderson and Alexander (3) use surgery on the phrenic nerve frequently to produce relaxation of adhesions. They crush the phrenic nerve except (*1*) when the adhesion is over a soft lesion, (*2*) when the adhesion exerts a horizontal pull, or (*3*) when there is active contralateral disease likely to require phrenic surgery. We have used a phreniphraxis in many cases of inoperable adhesions to produce some degree of relaxation but feel that if the adhesions are severable, a pneumonolysis is preferable. Archibald (4) prefers thoracoplasty for relaxation of pulmonary lesions.

The joker in determining whether a lung is relaxed or not is that not even a highly trained roentgenologist with the best films obtainable can predict with any degree of certainty or accuracy just how many adhesions there are in a pneumothorax or what are their visceral and parietal attachments or what their mechanical effect is on the diseased area of the lung. The roentgenogram does not even tell us with unfailing accuracy whether the cavity is closed or not. Consequently any method of making as certain as possible that the cavity walls will be approximated and remain so is valuable, provided that it does not entail too great a risk. Alexander (5) cites a case in point. He shows an X-ray film of a man with a pneumothorax with adhesions and a large cavity. He then shows the same man some months later after a phrenic crush and increased pressure in the pneumothorax. The cavity was apparently closed. Autopsy next day, however, revealed the cavity wide open. The X-ray film did not tell the true story here. In figure 1a is shown an imperfectly relaxed pneumothorax with cavity apparently closed. Figure 1b shows a marked spread with cavity in the right apex which

was previously clear. This patient subsequently had a right pneumothorax and bilateral pneumonolysis without complications.

Moreover, only a consideration of the present status of the patient, as was done in the patient shown in figure 1, is a false way of looking at the problem. An imperfectly relaxed pneumothorax may produce great symptomatic improvement, negative sputum and apparent cavity closure. Economic stability may also be maintained at the moment. The end results of the "cure," however, should be paramount in the eye of the physician's mind at least, and that eye should not be blinded by the glare of such great symptomatic improvement. The case for this long-sighted view is potent and demands our close attention.

In our clinic a follow-up of 44 patients who were receiving pneumothorax on January 31, 1934 reveals that of those with adhesions, in other words, with incomplete pneumothoraces, 37.5 per cent are well to-day, 20 per cent are unstable, 22.5 per cent are worse, and 15 per cent are dead, with 5 per cent unknown. Of those with complete pneumothoraces, 50 per cent are well, 25 per cent are unstable, and 25 per cent are unknown. Matson (6) cites long range figures in follow-ups of 850 patients who had had artificial pneumothorax. Of those who had complete pneumothoraces, 48 per cent are "apparently well," 20 per cent are arrested, and 21 per cent are dead. On the other hand, those patients who were unfortunate enough to have had incomplete pneumothoraces show only 13 per cent "apparently well," 13 per cent arrested, while 50 per cent are dead. Carter (7) emphasizes this as well. Peters (8) cites statistics comparable to Matson's in a review of 427 cases following pneumothorax. With complete compression 53 per cent are well and 24 per cent dead. With partial compression 25 per cent are well and 44 per cent dead. Certainly a mere glance at these figures should convince the most skeptical of the ultimate wisdom of securing complete collapse if possible. If this necessitates thoracoplasty or some packing operation, all well and good. However, a pneumothorax should be given every chance to achieve its end as it is probably the most efficient cavity closer we have. In this we agree with many others that an unrelaxed pneumothorax should not be allowed to run on and on, but should be converted into a complete, relaxed pneumothorax if possible or abandoned or a substitute considered.

In view of the well known shortcomings of the X-ray with reference to adhesions, it has become our policy to use thoracoscopic examination

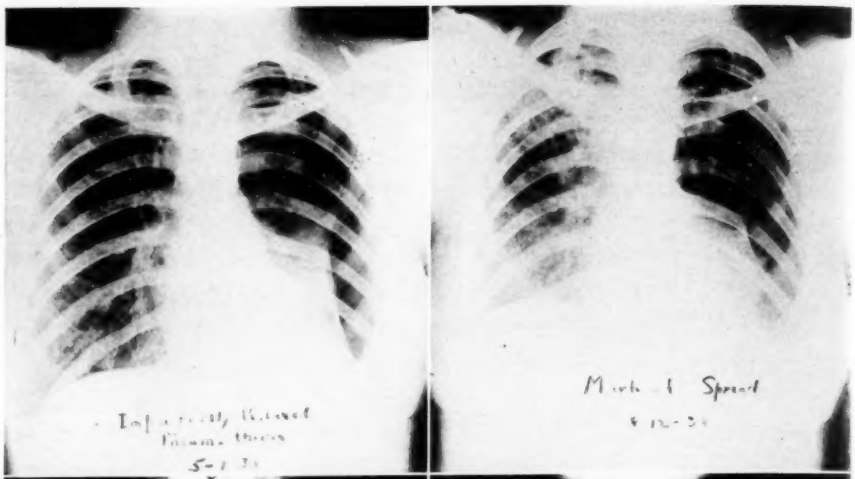

FIG. 1a

FIG. 1b

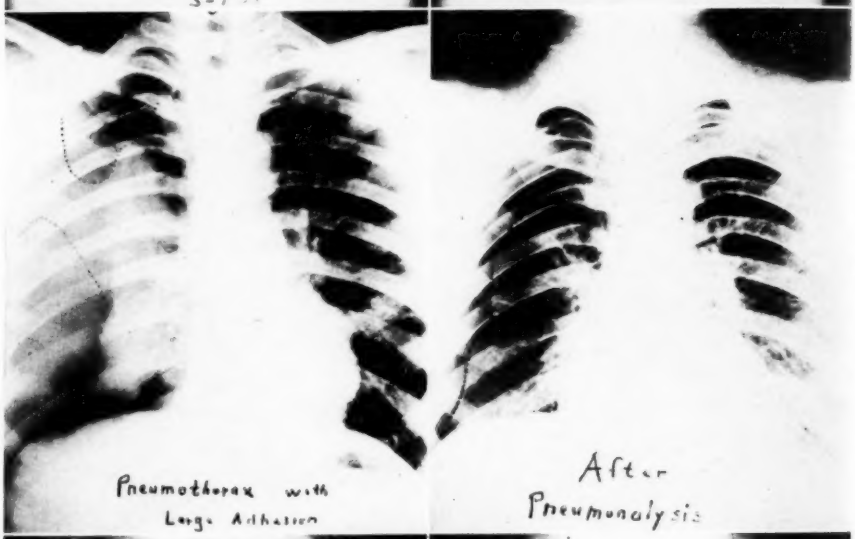

FIG. 2a

FIG. 2b

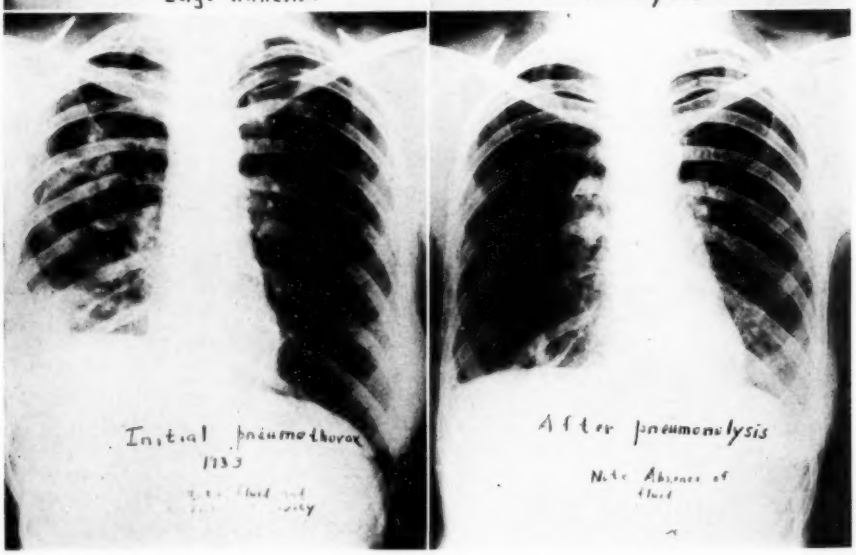

FIG. 3a

FIG. 3b

FIGS. 1a–3b

to make our decision as to whether a pneumothorax lung is completely relaxed or not. Naturally we do not inspect pocket pneumothoraces or those in which even the X-ray cannot mislead us, where there are large areas of lung plastered against the chest wall. Nor do we recommend inspection of those pneumothoraces which are from the first quite plainly free and show rounded lung outline without evidence of tenting or peaking. It is rare that one errs in these latter. We have been mistaken and have entered only one thorax in which we could find no adhesions after careful search. But where there is any doubt whatever, and this is to be interpreted liberally, we inspect the pleural space to determine the possibility of pneumonolysis before making further plans. In this we have not only the desire to convert unrelaxed pneumothorax lungs into relaxed ones, but have also in mind the future efficiency of the lung. It has been aptly put that the lung retains much more functioning tissue after expansion of a complete pneumothorax than after a thoracoplasty or some packing procedure, because some good lung is obviously always put out of function in the latter operations to permit of compression of the diseased area.

Maintaining a thin pleura also makes for a future efficient lung. Attempting a tension pneumothorax to relax a lung despite adhesions almost invariably produces a thick pleura. A successful pneumonolysis rarely thickens the pleura and obviates the necessity for high tension. Randolph (9) has emphasized this.

Prevention of complications is also a point to be remembered in the carrying out of a pneumothorax. It is an obvious point that it is the pneumothoraces with adhesions that have the most fluids—both serous and purulent. On January 31, 1934 there were 51 hemithoraces with pneumothorax at the Santa Clara County Sanatorium. On that date 14, or 27.4 per cent, had serous effiusion, 25.5 per cent being in hemithoraces with adhesions and 1.9 per cent without adhesions. Also on that date there were two tuberculous empyemata, or 3.8 per cent, one in a hemithorax with adhesions and one without adhesions.

FIG. 1a. Left pneumothorax with adhesions and apparent closure of cavity.

FIG. 1b. Marked spread with cavity in previously clear right apex.

FIG. 2a. Right pneumothorax with large lateral adhesion preventing relaxation.

FIG. 2b. Same case after severing the adhesion shown in fig. 2a. Three-stage operation.

FIG. 3a. Before operation. Apical adhesion with cavity open and fluid in the costophrenic angle.

FIG. 3b. Same case as in fig. 3a after operation. Note the relaxation, cavity closure, and absence of fluid.

On March 1, 1939 there were 155 hemithoraces with pneumothorax; in 51 of these pneumonolysis had been performed. On that date there were 7 cases with serous effusion, or 4.5 per cent as compared with 27.4 per cent five years ago. Now there is only one tuberculous empyema, or 0.64 per cent, as compared with 3.8 per cent five years ago. These figures show a remarkable difference. Of course, cases running at present may still have complications in the future—we cannot tell. The above figures compare complications on two dates five years apart.

It is a noteworthy point also that, of those hemithoraces with adhesions in 1934, 30 per cent had a spread to the other side during the period of pneumothorax. Hemithoraces without adhesions had no spreads whatever.

Stivers (10) has called to our attention the presence of ulcerated areas on the parietal or visceral attachments of a taut adhesion. These are caused by a mechanism similar to pressure necrosis, and it is easy to see how these raw, ulcerated areas can produce a serous exudate just as they do on a varicose ulcer of the ankle.

A thoracoscopy with pneumonolysis performed on any case of pneumothorax is like insurance—partial at least—against the complications of fluid and its sequelae of possible empyema and obliterative pleuritis. Thus for many reasons thoracoscopy is indicated.

OPERATIVE TECHNIQUE

It is not proposed here to go into the details of the operation or its technique, as that has been done in numerous articles in the literature. There are, however, a few points that have impressed themselves upon us as valuable additions and aids to a smooth operation. We follow in general the same technique used elsewhere. We use a two-cannula instrument, the Coryllos modification of the Jacobaeus instrument, equipped with the galvanocautery and the electrosurgical electrodes from a Davis-Bovie unit. Most of our work has been done with the galvanocautery. We find after experimenting that we prefer to use electrosurgery for coagulating and galvanocautery for cutting. In our series we have used the galvanocautery alone in 80 cases, electrosurgery alone in 5 cases, and both in 7 cases. We admit that both methods have advantages but have so far chosen to use the galvanocautery.

We are especially careful, by X-ray, fluoroscopy and preoperative refills, to make sure we insert our visual cannula into a lung-free and

adhesion-free space. The second or operating cannula is then inserted under direct visual, thoracoscopic control in order to avoid transfixing any adhesions or lung. By so doing we have missed all adhesions with our cannulas and have scratched the visceral pleura but once in a patient with a very narrow space.

On withdrawal one also can always inspect at least one of the parietal pleural wounds for bleeding before removing the final cannula.

Sponging out the cannulas and moistening the instruments with sodium citrate has prevented blood from coagulating in the cannulas and causing difficulty in freely moving both the 'scope and the cautery.

Anaesthetization of the parietal attachments of adhesions as suggested by Matson (11) is a valuable adjunct in sensitive patients. We have found it unnecessary in most of our cases. One danger, especially at the extreme apex, consists in too deep injection of the novocaine and possibly involving the brachial plexus. We once produced a three to five months' paraesthesia in a woman's hand as a result of this very thing.

Since our only empyema after an operation was purely pyogenic we have used sterile caps and masks, and even sterilized spectacles to prevent contamination of the proximal end of the 'scope.

Any fluid present before operation can be readily aspirated with a soft rubber catheter through one of the cannulas and possibly save the later insertion of a needle.

We always do a final thoracoscopic inspection through the operating cannula to avoid overlooking adhesions not visible through the 'scope in the visual cannula.

Decompression manometric readings are seldom taken as one knows from inspection and immediate fluoroscopy the state of compression of the lung. If cough is controlled and the patient is fluoroscoped again in twenty-four hours to determine the necessity for a refill, there is no danger of losing the space.

Large adhesions can be severed but it seems advisable to operate on these in more than one sitting. It is the wiser course to perform several short operations than to attempt too much at one time. The adhesion shown in figure 2a was severed in three sittings with the result shown in figure 2b. We have not hesitated to cut large adhesions but have not attempted the impossible and have realized that there are limitations to the procedure. Transillumination of adhesions with a special device or simply with the light of the thoracoscope is valuable in determining severability.

RESULTS

In the past twenty months we have inspected 96 hemithoraces in a total of 89 patients. This has been accomplished in 122 sittings. Of these 122 operations, 29 were thoracoscopies pure and simple; 92 were thoracoscopies and pneumonolyses; and one was thoracoscopy and biopsy. Radiologically, previous to operation, we had counted a total of 143 definite adhesions, and there were 12 cases in which the adhesions were too numerous or involved to count. A thoracoscopic count revealed a total of 210 adhesions plus 43 in the above 12 cases with multiple adhesions according to X-ray. The wide discrepancy in the figures is apparent. We were able to sever 169, or 66.7 per cent, completely, and a few additional ones partially.

TABLE 1

Mechanically and clinically successful	51 cases—53.1 per cent	63.5 per cent
Mechanically unsuccessful and clinically successful	10 cases—10.4 per cent	
Mechanically successful and clinically unsuccessful	6 cases— 6.2 per cent	36.4 per cent
Mechanically and clinically unsuccessful	29 cases—30.2 per cent	

The last figure includes 19 plain thoracoscopies.

TABLE 2

Mechanically and clinically successful	51 cases—66.2 per cent	79.1 per cent
Mechanically unsuccessful and clinically successful	10 cases—12.9 per cent	
Mechanically successful and clinically unsuccessful	6 cases— 7.7 per cent	20.6 per cent
Mechanically and clinically unsuccessful	10 cases—12.9 per cent	

The technical and clinical results are shown in table 1. This shows that only 63 per cent of the hemithoraces operated on were clinically successful. Others have reported higher percentages of clinical success. The reason is that we have looked into many hemithoraces in which nothing whatever was done but inspection, hemithoraces which others might not have inspected. These statistics, therefore, show a lower percentage of clinical success because of the excess of simple thoracoscopies.

Figured on a basis of hemithoraces in which some actual cutting of adhesions was done, our results are given in table 2. This gives us a total of 79.1 per cent clinical success and compares favorably with results elsewhere as shown in table 3.

Considering cavity closure by this method, we find that 58 of our 96 hemithoraces operated on contained what we considered a cavity; 39 of these 58 were operable and in 28, or 71 per cent of operable cases, were we able to close the cavity as judged radiologically. Of the total number with cavity we have thus been able to close 48.6 per cent. This seems to be worth the effort, the ability to close one out of two cavities.

Our first operation in each case has been performed on an average of 11.9 months after the initiation of the artificial pneumothorax. This figure is misleading, however, because on starting the procedure on

TABLE 3

Comparative results

Figures represent percentages

	SANTA CLARA COUNTY SANATORIUM 77 CASES*		FORSEE (12) 28 CASES		DUFAULT AND LAROCHE (13) 143 CASES		MOORE (14) 1,850 COLLECTED CASES	MATSON (11) 350 CASES	POWERS (15) 50 CASES	PETERS AND CORNISH (16) 88 CASES
Mechanically and clinically successful	66.2	79	53.8	61	55.8	60	75	70	85	
Mechanically unsuccessful and clinically successful	12.9		7.7		4.1					
Mechanically successful and clinically unsuccessful	7.7	21	27.0	39	15.9	40	25			
Mechanically and clinically unsuccessful	12.9		11.5		23.9					
Cavity closure	71.7									78
Worse	0						4.5			
Died	0						10.8			

* Pneumonolyses by Dr. Charles L. Ianné and Sanatorium Staff.

June 1, 1937 we operated on many long standing adhesions first. The period shortened as we caught up in our schedule. A more exact notion of the time is gained by the arithmetical mean of our cases which falls at six months. Even this is slightly high, and we at present operate about two months after initiation of pneumothorax.

COMPLICATIONS

The age of the pneumothorax seems to have no effect on the number of complications. Complications occur in pneumothoraces operated on in less than two months and in those operated on as long as forty months after initiation.

Our complications are not many. They are listed in table 4. It merits emphasis that all the complications that occurred were in 20 patients or 20.8 per cent of the total, leaving 80 per cent of patients entirely free of complications.

In operations which were purely and simply thoracoscopic inspections there were no complications whatever. In other words a thoracoscopic investigation in our hands to date has been totally without danger as far as complications are concerned. This point seems worthy of particular emphasis.

In addition to the figures above, citing what may be called disadvantageous results, we have found the following advantageous ones: namely, the absorption of exudate following operation and the lengthen-

TABLE 4

Complications

	CASES	PER CENT
Exudate		
Serous	7	7.1
Haemorrhagic	3	3.1
Empyema		
Staphylococcus albus	1	1.0
Tuberculous (occurred 7 months postoperatively)	1	1.0
Fever	13	13.5
Loss of space		
From obliterative pleuritis	2	2.0
From empyema	1	1.0
Thickened pleura	16	16.0

ing of periods between refills. Sixteen cases had serous fluid before operation; 10 of these cleared spontaneously immediately afterward and 2 others which were aspirated at the time of operation failed to form more fluid after operation. The average increase in time between refills was 4.5 days for all these cases figured on the basis of their refill schedules before operation and following stabilization after operation.

This last result is very important because it not only lessens staff hours of work, but saves a large number of insults to the parietal pleura by needle insertion. It lessens the number of opportunities for a refill accident. It facilitates refilling in general. And last but not least, it saves many a patient the psychic trauma of frequent refills.

As shown in table 3 the percentage of clinical success with the operation varies from about 60 per cent to 85 per cent. In our series we have done

well by more than 79 per cent, or 4 out of 5 patients operated on, exclusive of thoracoscopies. Our percentage of cavity closure is quite satisfactory. Due to inability to maintain complete pneumothoraces in some of our bilateral cases we have been unable to close a few cavities in hemithoraces operated on. We feel that complete compression will permit of closure of these cavities after the contralateral disease is more under control because we know from actual inspection that there are no

TABLE 5

Comparative complications

Figures represent percentages

	SANTA CLARA COUNTY SANATORIUM 96 CASES*	FORBES (12) 28 CASES	MATSON (11) 350 CASES		ANDERSON AND ALEXANDER (3) 111 CASES	PETERS AND CORNISH (16) 88 CASES	DUFAULT AND LAROCHE (13) 143 CASES	MOORE (14) 2,043 COLLECTED CASES	POWERS (15) 50 CASES
			Galvanocautery	Bovie					
Exudate:									
Serous	7.1	57.1	20.5	3.9		27.0		30.57	
Haemorrhagic	3.1		10.3	1.6			12.6	0.77	
Transient					27.9				46.0
Persistent					9.9				27.0
Haemorrhage	0	3.6			0	2.0	5.07	0.73	
Empyema:									
Tuberculous	1.0†	2.1			3.6		5.07	2.2	6.0
Pyogenic	1.0	21.3	26.4	2.8					2.0
Mixed	0				1.8		5.7	1.8	
Loss of space	1.0‡				1.2		7.2	0.29	
Obliterative pleuritis	2.0	3.6			3.6				
Traumatic pleurobronchial fistula	0	14.2				7.0	6.5		4.0
Pleurocutaneous fistula	0	7.1						0.14	
Death	0					1.0			

* Pneumonolyses by Dr. Charles L. Ianné and Sanatorium Staff.

† Occurred seven months later.

‡ From empyema.

more restraining adhesions to prevent that collapse. We have, however, closed all but 2 cavities in hemithoraces where the disease was unilateral.

Table 5 sets forth comparative complications. Serous effusion seems to be the most common complication. Our figure of 7.1 per cent compares very favorably with all the others except that of 3.9 per cent which Matson cites as his rate while using electrosurgery with the Davis-Bovie unit. This figure is truly remarkable and is something to strive for.

Our only tuberculous empyema occurred seven months postoperatively and can hardly be called a complication inasmuch as the patient did not even develop fluid for six months postoperatively.

Therapeutically the most serious complication encountered is that of loss of the pneumothorax space by obliterative pleuritis, as this defeats totally the very object of the operation and of the pneumothorax in the first place. This has occurred in 2 cases out of 96 and in both cases followed production of a serous effusion. With improvement in technique and less fluid formation it is hoped that there will be fewer or no cases with loss of space.

Taken altogether, an operation which offers 3 to 4 chances out of 5 of gaining clinical success and yet has such a minimal risk to life as compared with nonintervention, and serious complications in only 1 or 2 out of 50, is certainly worth the risk to the patient in such a serious disease as pulmonary tuberculosis.

COMMENT

In view of the results outlined, it seems obvious that this valuable operation has a definite place in our armamentarium. Granted that fact, we should put it to its full usefulness.

The only way of determining whether pneumonolysis is applicable or not with any degree of certainty is to perform thoracoscopic examinations on every patient with a pneumothorax who conceivably could be benefited by the operation. If one has done a thorough inspection and found the adhesions inoperable, he has no compunctions in abandoning it, but doubts always linger otherwise. In view of the apparent lack of danger associated with a plain thoracoscopy, as emphasized above, it can be advised without hesitancy as a routine measure. The figures cited previously from Matson, Peters and ourselves prove the definite value in long range results of a relaxed pneumothorax which is obtainable with safety by pneumonolysis.

From the standpoint of future health, therefore, the conservative measure is to advise thoracoscopy. From the standpoint of the alternative of a dangerous high pressure pneumothorax or of a thoracoplasty as a major operation which any patient is anxious to avoid if possible, thoracoscopy is again the conservative advice to give. Incidentally it is also advice the patient is apt to accept if told these alternatives.

The patient shown in figure 3 had her pneumothorax for more than four and one-half years with cavity questionably open and closed off and

on until thoracoscopy and pneumonolysis were eventually performed. She had at the very least four whole years of useless pneumothorax because of nonrelaxation of her lung due to the adhesion. During this time she was always fatigued at her work. Now with a complete pneumothorax and cavity closed, she feels well for the first time.

Laying aside, therefore, the purely medical reasons for thoracoscopy, we have the economic factor of the patient's time and money to be conserved. Both are served by thoracoscopy.

SUMMARY

1. A relaxed pneumothorax lung is to be desired in the treatment of pulmonary tuberculosis.

2. One way to obtain it is by closed intrapleural pneumonolysis, a relatively safe operation.

3. Thoracoscopy is the only sure method of determining whether pneumonolysis is possible.

4. Thoracoscopy has proved in our hands, to date, to be without danger to the patient.

5. Thoracoscopy is conservative because it aims at a relaxed pneumothorax lung, which in turn makes for greater conservation of life and economic resource.

The author wishes to express appreciation and thanks to Dr. Charles L. Ianné, Director of Tuberculosis, Santa Clara County, California and to Dr. L. P. Borden of the Sanatorium Staff for their kind coöperation and assistance in the preparation of this paper.

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THE EVOLUTION OF MODERN PNEUMOTHORAX MACHINES

I. Hydrostatic and Bellows-Type Machines

LOUIS R. DAVIDSON[1]

The earliest type of apparatus used to insufflate air into the pleural cavity was quite naturally a simple pump.

Hippocrates (1)[2] in his second book on *Affections* makes reference to the practice of introducing air into the chest to aid in the evacuation of pus from the pleural cavity. A detailed description of the procedure employed is not available, but it appears that a tube was inserted into the chest and air forced through it by expressing a simple bladder.

Hewson (2), in the 18th century, induced artificial pneumothorax in experimental animals by cutting down to the pleura and then inflating air into the pleural cavity by means of a simple bellows.[3]

Davy (3) at a later date, experimenting with dogs on the absorption of different gases from the pleural space, used a double bellows ". . . furnished at one extremity with a stopcock and at the other with a small trocar, both air tight."[4] An incision was made into the pleura and the trocar introduced. The external wound was then closed by a suture and the gaseous contents of the bellows forced into the pleural space.

A number of experimenters in the 19th century made similar investigations on the composition of air in the pleural cavity. They introduced air into the thorax by means of some form of bellows.

Boudens (4) in 1836, treated pulmonary wounds by introducing air into the chest. By means of a pump he insufflated sufficient air to create a pressure of two to three atmospheres, and occasionally even higher.

Parker (5), in his treatment of certain types of empyemata, systematically introduced filtered and carbolized air into the pleural cavity. He combined this with the aspiration of pleural effusions. His apparatus

[1] Sea View Hospital, Staten Island, New York.

[2] All references in part I of this article will be found in the Bibliography at the end of part II in the November, 1939 issue of the Review.

[3] Hewson does not actually describe the instrument used to blow air into the chest, but there is little doubt that he used the simple bellows.

[4] Page 501 of *Philosophical Transactions*, 1823.

consisted of a simple hypodermic syringe fitted with an elastic bulb and some carbolized cotton wool which served as a filter. The air was injected into the chest through a cannula inserted through an intercostal space.

Hicks (5) modified Parker's apparatus by attaching a manometer to the side arm of the cannula, thus making possible the reading of intra-

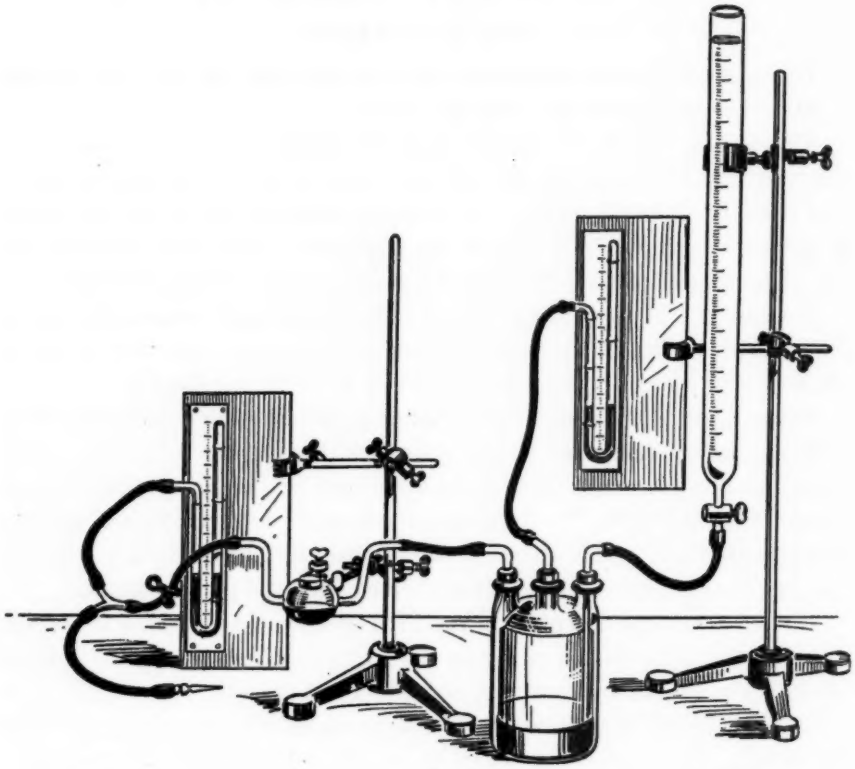

Fig. 1 WEIL

pleural pressures. A second modification by Hicks provided for simultaneous irrigation of the pleural cavity.[5]

Weil (6), as early as 1879, used a surprisingly modern apparatus (figure 1) to induce pneumothorax in dogs and rabbits while engaged in his investigations of intrapleural pressures. He used the hydrostatic pressure of a liquid column to displace air into the pleural cavity.

[5] A detailed description of Hicks's apparatus is not available.

His apparatus features a graduated cylinder filled with water communicating with a second chamber filled with air and situated at a lower level. A tap controls the flow of liquid from the upper to the lower chamber, and the air displaced from this is led to the pleura through a delivery tube and cannula. Two water manometers are incorporated: one connected to the lower chamber measures the pressure in the system, and the other attached to the delivery tube serves as oscillometer and to measure intrapleural pressures.

The cannula was introduced by first incising through the skin and superficial muscles and then piercing the underlying tissues and parietal pleura. Entrance into the free pleural space gave rise to oscillations and negative readings in the water manometer. Then by opening the communication between the two chambers, pneumothorax was induced with a measured volume of air.

Weil clearly recognized the value of the manometer, both in measuring the intrapleural pressure and as oscillometer to indicate the location of the needle. He even aspired to obtain permanent records of intrapleural pressure variations, and to this end he connected a Bourdon-Sanderson cardiograph to the delivery tube and registered tracings on a kymograph.

Here then we have the elements that epitomize a most modern instrument dating back to some three years before Forlanini (7) first proposed to treat pulmonary tuberculosis with artificial pneumothorax. But Weil was concerned mainly with spontaneous pneumothorax and was investigating the different types which he endeavored to simulate in his experimental animals by inducing penumothorax artificially.

The apparatus described by Potain (8, 9), in 1888, for the treatment of hydropneumothorax consists of two parts; an aspirator with a manometer attached, and a pneumothorax machine similar in principle to that of Weil. It consists essentially of a needle, fine rubber tubing and two communicating chambers. Hydrostatic pressure is employed to displace the air from the gas chamber through a carbolized solution and a cotton filter into the chest. A clip on the rubber tubing controls the flow of liquid into the gas chamber so that sterile air is made to enter the pleural cavity as rapidly as the effusion is aspirated and, in this way, a pressure of about 6 to 7 mm. of mercury is maintained.

The stage is now set for the advent of Forlanini and Murphy.

Staunchly convinced that the interruption of the function of the diseased lung by the establishment of an artificial pneumothorax would control pulmonary phthisis, Forlanini's next step was to produce an instrument to put his idea into practice. In his publications he makes

not a single reference to any earlier apparatus used for the insufflation of air into the pleural cavity.

His first apparatus (figure 2a) (10, 11)[6] consists of two glass cylinders, each of 500 cc. capacity, fixed at one level by means of a glass tube connection. One cylinder is graduated in cubic centimetres and contains the gas to be injected; accordingly this was designated "gasometric chamber."[7] The other cylinder is filled with water or antiseptic solution[8] and was designated "liquid

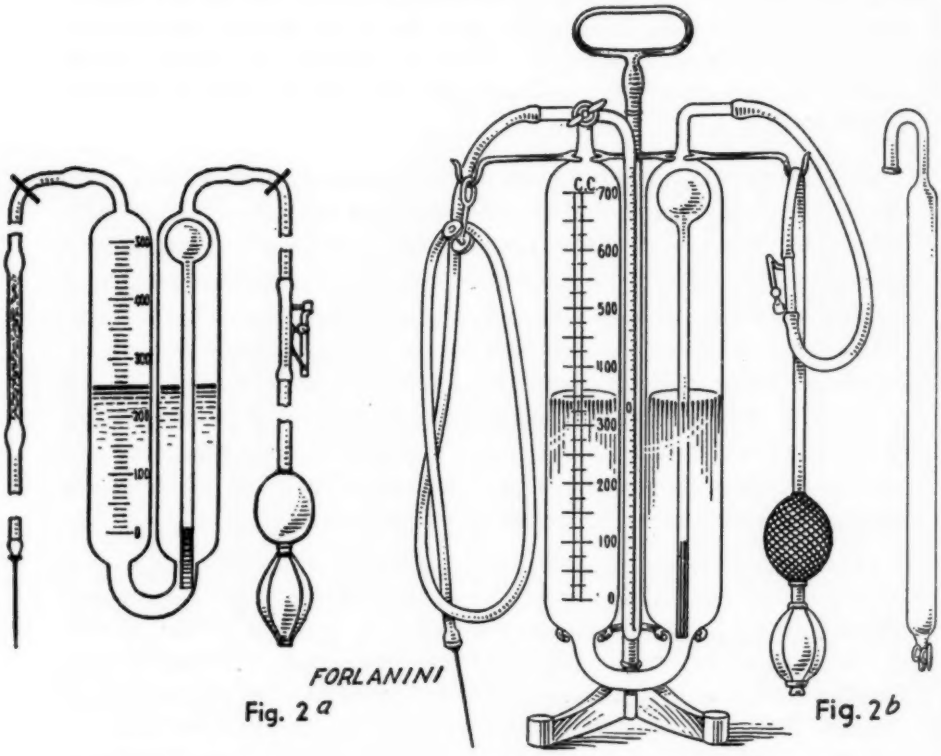

Fig. 2a Fig. 2b

reservoir." Pinch clamps serve to open or close the instrument. The liquid reservoir is connected through rubber tubing with a Richardson double balloon, while the gasometric chamber is connected with a delivery tube and filter to the needle.

[6] This apparatus appeared in the illustrated catalogue Zambelli, Turin, as early as 1897.

[7] Forlanini first used filtered air but soon changed to pure nitrogen, having found that the oxygen of ordinary air was absorbed all too rapidly.

[8] A solution of sublimate was used.

It will be pointed out that Forlanini used no true manometer in this apparatus, but that he had an inverted closed tube inside the liquid reservoir which, he claimed, showed all he needed to know about pressure readings. The rise and fall of its liquid column indicated when the needle pierced the parietal pleura, and the height of the column at any time was equivalent to one-third the pressure of the system in centimetres of water.

A second apparatus (12) served for the production of nitrogen, or, more accurately, furnished oxygen-free air which was chemically produced by the reaction of atmospheric air with pyrogallic acid and *liquor potassae*. This gas was used to charge the gasometric chamber of the pneumothorax machine and was introduced by means of hydrostatic pressure. A column of water contained in a fluid reservoir displaced the nitrogen from the chemical chamber through a cotton wool filter and into the gasometric chamber, forcing the contained sublimate into the liquid reservoir. The apparatus was now ready for use and, after introducing the needle into the pleural cavity, the pinch clamp was released, allowing the sublimate to gravitate into the gas chamber, displacing the nitrogen into the chest. In this manner, half of the nitrogen can be displaced by hydrostatic pressure, but after the liquid reaches the same level in both cylinders, the Richardson balloon has to be used as a bellows. This drives the fluid before it into the gasometric chamber and thus displaces the rest of the nitrogen into the chest. This instrument, therefore, employs both hydrostatic and bellows principle, but it is usually designated as a bellows type of apparatus because the two chambers are fixed at one level.

Murphy's apparatus (figure 3) (13), 1898, employs the hydrostatic principle exclusively. It consists likewise of two intercommunicating chambers, one for the gas and the other for the liquid, but the latter chamber is not fixed and can be raised to any desired level so that its contents may be completely evacuated by hydrostatic pressure alone. The gas chamber is graduated in cubic inches. Like Forlanini's, this apparatus was first filled with nitrogen gas by connecting the gasometer to the source of the gas—in this case a cylinder containing nitrogen under pressure. By opening the valve of the cylinder, the gas flows into the graduated chamber, displacing its contents (water) into the reservoir bottle. The apparatus is now charged and ready for service. By simply placing the reservoir bottle on a block, thus raising its level above that of the gasometer, a hydrostatic pressure is obtained which forces the gas from

the gasometer through a delivery tube and to a cannula which is introduced into the chest.[9] Like Forlanini's machine, this too had no manometer.

The incorporation of the manometer in the pneumothorax machine marks a significant step forward in the evolution of this instrument.

Saugman (14), in 1904, improved Forlanini's apparatus by adding two manometers—a water manometer for common use, and a mercury manometer for high positive pressures.

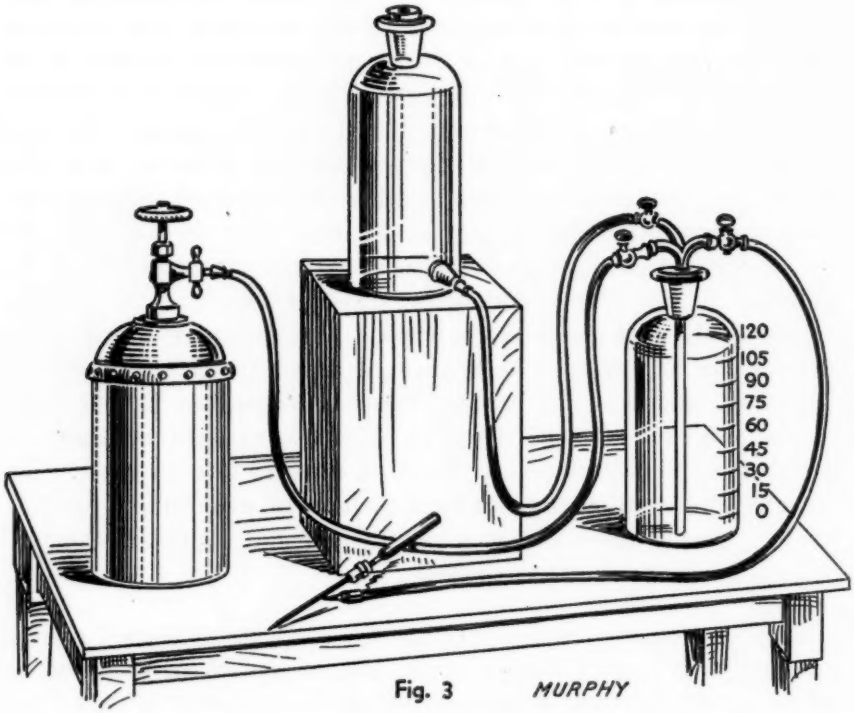

Fig. 3 MURPHY

Brauer (15), in 1906, on the other hand, improved Murphy's apparatus by the addition of two similar manometers.[10]

[9] To induce pneumothorax, Murphy made an incision through the skin and subcutaneous tissue and then introduced a trocar and cannula. His method is known as the "Schnitt" or "incision" method in contradistinction to the "Stich" or "puncture" method used by Forlanini.

[10] Brauer further incorporated in his apparatus what might be termed a spy glass. This consisted of a short piece of bent glass tubing of small calibre, situated within the liquid

It must not be supposed, however, that the use of manometers to determine intrapleural pressures had not been known before this time. Mention has already been made of their use in certain pre-Forlanini instruments. It will be of interest at this point to digress and to review briefly the evolution of intrapleural manometry.

As early as 1820, James Carson (16) in Great Britain had used manometers for this purpose, in the course of his researches on the elasticity of the lung in animals. He demonstrated the presence of a negative intrapleural pressure and measured this as well as the intraälveolar pressure in experimental animals. His technique was to insert the lead from a manometer into the trachea. He then opened the chest wall, and the collapsing lung registered on the manometer a positive pressure which he inferred to be equal to the elastic force of the lung.

At later dates Donders, Perls, *et al.* (6), using similar techniques, confirmed Carson's findings.

Powell (17) demonstrated postmortem the presence of positive pressures in a case of tension pneumothorax. He used a trocar with a branched cannula to which he attached a water pressure gauge. He suggested that this method might be employed in the living.

Von Quincke (18), in 1872, adopted this suggestion, and thus marked the beginning of manometry in spontaneous pneumothorax. Peyrot, Leyden and Frankel extended the application to pleural effusions (17).

Weil (6, 19), as we already have seen, used two water manometers on his apparatus. He points out that a negative pressure is recorded the moment the needle enters the pleural space. He advocated the use of the manometer in differentiating between the various types of spontaneous pneumothorax.

Aron (27, 18), some years after, published a detailed study of spontaneous pneumothorax.[11] He enlarged upon Weil's work and confirmed the value of manometry. Aron, after trying mercury and water manometers, chose glycerine to measure intrapleural pressures.

The value of manometry became clearly appreciated and, before the

reservoir, and leading directly from the air inlet. A drop of fluid was placed within the tubing and indicated, by its shifting, whether or not gas was flowing into the chest. As the nitrogen from the gasometric chamber was displaced into the pleural cavity, air entered through the inlet to replace the fluid into the liquid reservoir. The flow of this air disturbed the drop of fluid in the spy glass and so indirectly indicated that nitrogen was entering the chest.

[11] E. Aron, *Die Mechanic und Therapie des Pneumothorax*, 1902.

turn of the 19th century, its use was adopted by many clinicians[12] in spontaneous pneumothorax.

Potain, as was mentioned before, used a mercury manometer in his aspiration apparatus, and Hicks made this addition to Parker's instrument.

Forlanini evidently knew that the manometer had been employed by some of his predecessors to measure intrapleural pressures. He quotes Parker's article in his original work (9, 21) and the reader will remember that this article also referred to the attachment of a manometer to the Parker apparatus by Hicks. Furthermore, it is unlikely that Forlanini did not know of the use of manometry in spontaneous pneumothorax. Forlanini (22) moreover stated that in his first apparatus,[13] before 1890, he actually used a graduated manometer, but later excluded this feature as an unnecessary complication. He insisted, until 1910, that his internal tube inside the liquid reservoir (figure 2a) served as a manometer and gave him all the information necessary about intrapleural pressures.

Murphy evidently was not very well acquainted with the literature and makes no mention of intrapleural manometry.

Saugman and Brauer realized the value of manometry and since then practically every inventor has incorporated some form of external manometer in his pneumothorax apparatus.

Now that we have traced the early development of the essential elements of the modern apparatus, we can proceed to an enumeration and a critical study of those which followed. An amazingly large number have been described in the last quarter of a century, each inventor striving to make his machine more simple in design, inexpensive and accurate in construction, more efficient in application, facile in operation and more portable than the ones before him. But despite their apparent diversity, there are relatively few machines that really depart from the fundamental principles that we have found in the apparatuses of Forlanini and Murphy. In general it might be said that each model reflects, in a most singular manner, those points relative to pneumothorax technique being of greatest importance in the estimation of its inventor. Accordingly, some stress the meticulousness of measurements more than others, and so on.

[12] Among these may be mentioned Seifert, Ewart, Mennier, Mar and Gebbard, West, Desbiez, Beclere and Buddinger—quoted by Emerson (20).

[13] We are unable to find any direct reference or description of this early instrument.

Several distinct trends, however, can be traced in the evolution of the modern machine and its method of application. First of all, from the once universally used nitrogen gas, there has been a gradual but definite change to filtered air as the gas of choice. Secondly, there seems to be a tendency to go from the bellows type to the hydrostatic type as the preferred system of driving air into the chest, and most of our best machines to-day combine both fundamental principles.

For clarity of presentation we shall try to group together the outstanding types, according to the mechanical principle which each employs, rather than to any strict chronological order. Whenever claims for priority arise, these are automatically decided by the date of the publication in which the apparatus was first described. This survey covers the literature available in English, German, French, Italian and Spanish, though articles from other languages were often found translated into one of the tongues just mentioned. It is quite possible, we are certain, that some articles may have escaped our search.

Pneumothorax apparatuses may be conveniently classified into one of the following groups:

I. *Hydrostatic machines:* those that employ the gravitational force of a column of liquid to displace the gas used for the pneumothorax.
II. *Bellows-type machines:* those that employ the compression of air, whether it be by means of a pump, rubber bulb or bellows, in the stricter sense, to force fluid from one chamber into a second.
III. *Fluid-free machines:* those that do not, as the name implies, employ any liquid for air displacement.
IV. *Continuous reversal machines:* those that employ some sort of commutation valve which makes the apparatus of unlimited capacity. These in turn may be of each of the first three types.

Often the line of demarcation is difficult to draw, for many of the hydrostatic machines use a rubber bulb to accelerate gas insufflation and also when high positive pressures are required. On the other hand, there are just a few machines which would not fit into any of the four groups mentioned and therefore we shall describe them here.

Lemke (23), a pupil of Murphy in America, was one of the first to apply artificial pneumothorax therapy, and he used an apparatus like the modern spirometer (figure 4). The inlet tube was connected with a nitrogen tank, and opening this connection would fill the apparatus by raising the inverted hollow cylinder. Then, closing the inlet valve and opening that of the outlet,

the inverted cylinder would fall gradually and give a gentle pneumothorax. The cylinder is graduated to measure the volume of gas used. No manometer was employed.[14] Murphy and Krencher (24) used the Lemke apparatus and pointed out the desirability of injecting the gas into the chest with scarcely any positive pressure. They considered it unjustifiable to force the gas in. A mercury manometer, attached to the delivery tube, was incorporated in this apparatus.

Foster (25), in 1916, presented a similar machine also having a mercury manometer.

Bethune's (26) apparatus is the modern version of the Lemke type. Both the inverted inner cylinder and the upright outer cylinder are of unbreakable,

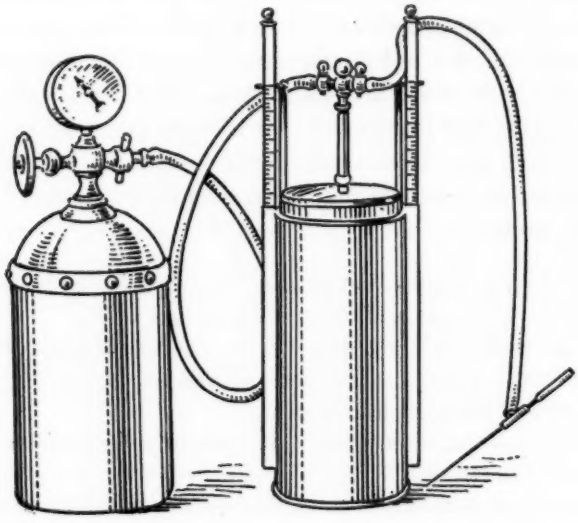

Fig. 4 LEMKE

transparent material. The apparatus is filled by opening the inlet valve and raising the inner cylinder. It has a simple water manometer connected in parallel with the delivery tube.

HYDROSTATIC MACHINES

We already have given a brief description of the first four apparatuses of the hydrostatic type, for such are Weil's, Potain's, Murphy's and Brauer's.

[14] The technique of induction was as follows: incision was made through skin and subcutaneous tissue; then a free needle was inserted and the patient asked to take a series of inspirations. As the needle pierced the parietal pleura a noise was heard caused by the inrushing air.

Lexner (27), in 1907, produced a model which offered a slight improvement upon Brauer's. He attached to the gas chamber a T-shaped joint with a stopcock, so that by turning the key he could measure independently either the intrapleural pressure or the pressure of the instreaming gas.

Wellman (28), in 1908, described another variation of Brauer's instrument. He used a tonometer originated by von Recklinghausen instead of the ordinary manometer.

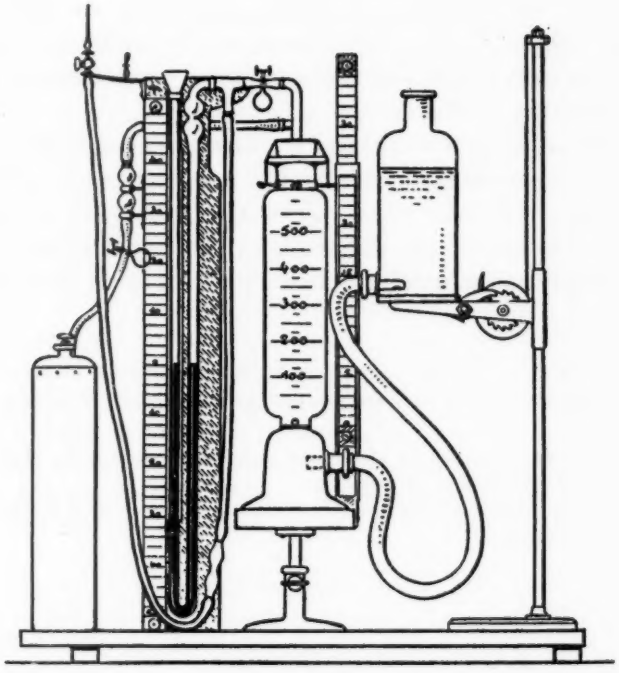

Fig. 5 KUSS

Kuss (29, 30), in France, presented in 1910 an apparatus (figure 5) which at once won wide popularity and precipitated much criticism, leading often to heated controversies, especially in his own country. The apparatus, at first glance, appears fundamentally the same as that of Murphy's, except that the communication between the two chambers is brought about by means of a thick-walled rubber tube of generous length so that the liquid chamber may be raised above or lowered below the level of a fixed gas chamber, and thus serve in the first instance for insufflation and in the second for deflation. But what aroused discussion were the dimensions of the gasometric chamber as prescribed by Kuss.

He maintained, and proved it quite convincingly with the aid of involved mathematical calculations and formulae based on gas laws, that a gas chamber 6 cm. in diameter serves at once as an ideal manometer and gas chamber.[15] When liquid rises into this chamber, the column is of such proportions as to absorb all disturbing oscillations usually seen in the familiar water manometer, and records only the real intrapleural pressure.[16] The latter, Kuss maintains, is not at all the arithmetical mean of the highest and lowest manometric excursions, as most observers erroneously estimate. He incorporated a conventional U-type water manometer as well, but this he used only as an oscillometer to guide him as to the location of the needle.

To get the real mean intrapleural pressure, a special technique is used; this consists of lowering or raising the liquid chamber until there is no further flow. A brief pause allows the equilibrium of gases to be established, whereupon the difference in the liquid levels in the two chambers measures the true intrapleural pressure in terms of centimetres of water.

Many modifications of this apparatus appeared at later dates. The inventors were chiefly concerned with improving the mechanism of raising and lower-

[15] A critical study of the details of the mechanico-physical principle of this apparatus appears in Revue de Tuberculose, 1925, *6*, 78.

[16] The following formula is an expression of pressure changes as a function of volume variations in a gaseous mass:

$$h = \frac{nH}{2(V + n) + \frac{\pi d^2}{4}(H + 2a)}$$

Where:

V = volume of a given pneumothorax in quiet expiration
n = increase in volume of the same pneumothorax at the end of an inspiration
d = internal diameter of the manometer
a = the height above the zero mark in the closed branch of the manometer
H = atmospheric pressure (760 to 1,000)
2h = the amplitude of the oscillations of the liquid level in the manometer due to the respiratory movements.

This formula shows that:

(1) The amplitude of the excursions of the liquid level diminishes as the diameter of the manometer increases (in the denominator figures the diameter of the manometer is elevated to the square and multiplied by a value slightly higher than atmospheric pressure).

(2) The amplitude also depends on the value of the pneumothorax and on the size of the closed space which lies above the liquid level.

(3) Very small variations of volume in the pneumothorax cavity determine notable variations in the intrapleural pressure (in the numerator figures the increase of volume of the pneumothorax cavity is multiplied by atmospheric pressure).

ing the hydrostatic chamber and this has been achieved by a wide variety of devices ranging from a rack and pinion arrangement to an elaborate system of multiple pulleys and counterweights as will be seen later.

Deneke (31) in Germany (1911) and Robinson and Floyd (32) in this country (1912) presented modifications of the Kuss apparatus. The fundamental principle remains the same—the hydrostatic chamber being movable and the gas chamber fixed.

Bonninger (33), in the same year, presented a simple hydrostatic apparatus. The contents of the gas chamber, before passing into the chest, are made to bubble through an antiseptic solution, acting as a filter and germicide at the same time. The reservoir consists of a simple irrigator. This entire apparatus can be readily assembled from parts which are available in any laboratory.

Pearson (34), in 1913, described a hydrostatic instrument which has the reservoir set on a shelf so that the weight of the hydrostatic column can be changed by altering the height of the shelf.

Hamanon and Sloan (35) made a modification of Brauer's apparatus. The nitrogen from the tank is bubbled through a wash bottle containing a solution of sublimate before entering the gasometric chamber. Two manometers are incorporated, one of water and one of mercury, and are interchangeable by the turn of a three-way stopcock.

Woodcock's (36) apparatus of the same year employs nitrogen generated from air by means of a chemical reaction.[17] The author suggests that hot water be used in the reservoir so as to warm the gas. A water manometer is used which is so constructed as to act as a safety valve. It permits pressures no higher than ten inches of water.

Lister (37), in 1914, presented a modification of Woodcock's machine, which generated both oxygen and nitrogen. Though this is an awkward and cumbersome unit, it has interesting features of mechanical construction. A so-called regulator with a pointer indicator enables the operator to switch from one gas to the other by a mere turn of the pointer. When turned to "closed" the manometer is automatically thrown into communication with the chest and readings are thus obtained. This feature has been carried over to many modern apparatuses, especially those of the continuous reversal type.

Bang (38) described an apparatus which features, in addition to a water manometer for intrapleural pressures, a Marey tambour placed in communication with the delivery tube. A needle and lever system from the diaphragm of the tambour record, on a kymograph, the fluctuations

[17] Pyrogallate solution.

of the intrapleural pressure. Thus, detailed graphic records are made available which show that a characteristic curve is produced when the needle is within the pleural space.

Davies (39) criticized Kornmann's apparatus which employed the bellows principle. He advised that the gas be injected in a gentle, steady stream and stated that this could be achieved only by hydrostatic displacement. His apparatus features two hydrostatic liquid reservoirs, one of 700 cc. capacity and the other of 300 cc. capacity. He used a water manometer only.

Etlinger (40) offered a simplification of Davies' machine. It had only one reservoir and two gasometric chambers, one for oxygen and the other for nitrogen.

Adams (41) criticized Etlinger's instrument for driving the gas at too high a pressure and pointed out its dangers. He placed his reservoir at a lower level so that no pressure could be obtained higher than that of 30 cm. of water.

Mace (42) described a combination manometer-safety-valve which prevents the use of pressures higher than those desired. It consists of a wash bottle with a rubber stopper having three holes. Two serve for inlet and outlet glass tubes respectively, and these do not reach the water level in the bottle. The third opening, in the centre, is for a glass tube that terminates below the water level. This tube is perforated along its wall at a given distance above the water level: the liquid level in the shaft of the central tube serves as a manometer, but, as this level rises with increasing pressures, the perforation is reached and the apparatus ceases functioning. This device, of course, may be applied to any apparatus. The following year Mace described an instrument (43) which he termed a modification of Forlanini's. He placed two intercommunicating chambers on a ring stand and added his safety manometer.

Morgan (44) found fault with the accepted technique for inducing pneumothorax, and in 1914 offered a machine which would obviate the inconveniences he pointed out, that is, the interruption of the flow of gas to get pressure readings, and the lack of a means of indicating whether or not the gas is flowing at any given instant. His apparatus has two manometers: the one nearest the gasometric chamber indicates at all times the gas pressure in this chamber, whereas the second, nearer the chest, indicates an intermediate pressure from which the intrapleural pressure may be calculated.

A modification (45) of this machine several years later features a regulator contrivance interposed between the two manometers, controlling the rate of

flow of the gas. The chief claims for this apparatus are: ample oscillations are shown throughout the procedure; it shows at all times whether there is a flow of gas[18] and in what direction; the rate of flow can be controlled, and the operation is never interrupted for intrapleural pressure readings.

Asher (46) described a simple arrangement using a fountain syringe from which water flows into an inverted graduated bottle containing nitrogen. A three-way stopcock admits the gas either to the chest or to the manometer, and raising or lowering the liquid reservoir provides the necessary hydrostatic pressure.

Vrooman and Wittich (47) modified the Floyd-Robinson apparatus by merely putting the reservoir chamber on a shelf movable up or down.

Stahl (48), in 1915, presented an instrument employing the hydrostatic principle but deviating from the ordinary arrangement. It consists of two chambers situated one within the other. The inner chamber is charged with nitrogen from a tank, thus displacing the fluid into the outer chamber. When the connection between the two chambers is opened, the liquid displaces the gas and this is led through tubing and needle to the chest or to the manometer. The apparatus incorporates the double manometer system. Communication between the two water manometers is made through a small needle-opening fitted with a special pin control valve.

Dobbie (49), in 1916, described an apparatus consisting of three bottles: a liquid reservoir, 1,500 cc. capacity, and two gas chambers, one for oxygen, 250 cc. capacity, and a second for nitrogen, 1,000 cc. capacity. A three-way stopcock provides the desired connection between the gas chambers and the needle in such a way that the manometer is always connected with the needle. The liquid reservoir is movable up or down by means of a crank and ratchet arrangement.

Montgomery (50), in 1918, described a simple apparatus easily improvised. By pouring water through a funnel into a gas bottle, air is displaced and sent into the chest through the familiar rubber tubing and needle. By attaching a two-way adaptor and aspirating syringe to the needle, he provides a means of aspirating fluid from the chest—which is received into a drain bottle through appropriate tubing—and replacing the fluid with air, thus obviating the necessity of another needle puncture.

Waller (51), in 1919, and Wolley and Sheridan (52), in the following year, described simple hydrostatic machines, similar to most others of this type.

A step forward was marked in 1921 when Hartmann (53) first described an instrument of the hydrostatic type in which both chambers

[18] As long as gas flows, no matter how slow the rate, the intermediate manometer shows a lower pressure, while with a one-manometer system one cannot tell if gas is flowing before an appreciable change in the fluid level has taken place.

are movable up and down. Hitherto, only the liquid chamber was raised or lowered according to whether pressure or suction was desired.

Gorriti (54) claimed priority for this innovation when he offered an apparatus of the same description in 1922. For aspirating pleural effusions he attaches a drain bottle.

MacMillan (55) presented in 1922 what he called a simplification of the Brauer-Spengler machine and a modification of the Murphy apparatus. Actually it employs an irrigation flask to displace air from a gas chamber. He advises the use of warm water to heat the gas.

Hofvendahl (56) criticized the Forlanini-Saugman apparatus for not permitting a smooth, regular flow of gas, and found the same objections to the Murphy-Brauer variety. He preferred the Lindhagen[19] type and presented a modification of this to make it smaller and portable.

The apparatus consists simply of the customary two chambers, the liquid reservoir being fixed at a level higher than the gas chamber. A cock regulates the rate of flow from the former to the latter. To aspirate the chest a negative pressure is created by allowing fluid to run out from the air chamber through a suitably placed outlet.

Lauret and Aumont (57) described an instrument consisting of a gas chamber in the form of a bottle and a rubber stopper. It has a cock at the bottom. The rubber stopper provides openings for a dropping funnel, delivery tube and manometer tube. Antiseptic solution is poured in through the funnel. In the tube leading to the manometer, a Marey compensatory valve is inserted which is supposed to give true readings of intrapleural pressures.

Woodcock and Fernandez (58) described a hydrostatic apparatus incorporating the Morgan double manometer system. A differential regulator is situated between the two manometers to control the rate of flow.[20] The movable hydrostatic chamber is set on a metal frame.

Goussel (59), in 1924, presented a model in which the hydrostatic chamber can be raised or lowered on a pulley arrangement.

Breger (60) offered a modified type of the movable liquid chamber apparatus. He provided a rack which permitted the latter to be moved up or down 30 cm.

[19] We were unable to locate a description of this apparatus in the literature.

[20] The authors criticize Morgan's claim that it is possible to estimate intrapleural pressures with exactness by the use of mathematical formulae in the double manometer system and offer several arguments which show that certain factors tend to vitiate the accuracy of the calculation.

with respect to the fixed chamber. In other words, it can easily be converted into an aspirating apparatus.

Kouchnir (61), in the same year, described another variety of the same type, but it shows no advance whatever. In fact, it is primitive inasmuch as to drive the liquid back from the gas chamber to the liquid chamber compression with a rubber bulb must be used.

Bonnamour (62), in 1925, offered nothing new in the way of mechanical advancement when describing still another variety. His movable chamber must be raised or lowered by hand. But there is something of interest in it: he advised bubbling the gas (he used nitrogen) through an emollient antiseptic solution[21] which he claims reduces pleural effusions to the point of rarity. He controls the flow of gas by means of a Mohr thumb clamp attached to the rubber tubing connecting the two chambers, for he claims that the gas pressure within the gasometric chamber is dependent upon the rate of flow of the incoming liquid and not upon the difference in fluid levels, as is generally believed. An anaeroid manometer is constantly in communication with the gas streaming into the chest.

Brown (63), in 1925, presented an instrument which does not differ in any way from the foregoing.

Riviere (64) recommended the Lillingston-Pearson apparatus which is of the same type.

Stokes and Stabo (65) favored the above apparatus and presented one with a negligible modification.

Marshall (66), in 1930, used a rubber bag of the "hot water bottle" type as a hydrostatic reservoir chamber, and three filters to purify the air.

Beynon's (67) apparatus is likewise of the same type as the familiar two-intercommunicating-bottles system. He recommended it for its inexpensiveness.

Natin and Rovere (68), in 1931, described an instrument that has a trivial modification of the Kuss machine.

Elman and Wright (69) presented an apparatus which features a switch as the only part having to be manipulated during the operation. A water valve controls the flow of liquid from the upper to the lower chamber.

[21] This solution was of the following composition:

essence of birch essence of thyme citron water lavender amyl acetate	in picric acid

Dobszay and Salamon (70) offered an apparatus featuring a metal regulating disc controlled by means of a lever. Its simplicity of operation makes it especially suitable for children, the authors feel.

Cutler (71), in 1933, modified the popular Robinson instrument. He replaced the two separate stopcocks by a single one which, by a simple turn of the key, puts the chest into communication with the manometer in one position and with the gas chamber in the other.

Bunta (72), in 1934, presented an apparatus not greatly different from the others. It provides for the inclusion of a chamber with pyrogallic acid solution. Whenever oxygen-free air is desired, the air is bubbled through this chamber before entering the chest. Foreign particles are thereby removed also. The water manometer features a reserve chamber which receives any overflow of liquid.

Hatfield and Tremble's (73) model has two metal chambers, the movable one sliding upon a metal rod. The air chamber is not graduated but an air volume indicator is fitted to it and gives direct readings on an adjacent scale. The operation is controlled by means of a three-way valve situated at the top of the air chamber. By turning a lever, the valve may be placed in any one of six positions. Three of these keep the system closed, while the other three allow the following communication:

1. Air chamber—atmosphere
2. Manometer—atmosphere
3. Chest—manometer—air chamber

The water manometer has a zero adjuster, obviating the necessity of replacing the liquid that is lost by spilling or vaporization. This is achieved by means of a rubber bulb reservoir controlled by a set-screw adjuster. Compression or relaxation of the bulb brings the liquid to the zero mark.

Galarza (74), in 1934, made a simple modification of the Kuss apparatus, rendering it smaller and lighter.

Munie (75), in 1936, presented another modification of the Kuss instrument. The chief improvement lies in an elaborate system of pulleys and counterweights controlling the upward and downward movement of the hydrostatic chamber.

Chaise (76) likewise described a modified Kuss apparatus. This instrument is more compact and portable. A folding stand is used for the movable flask. Instead of the simple U-tube manometer, a double U-tube manometer is employed to decrease the standing height of the manometer by almost one-third.

Bramkamp (77), in 1936, presented a familiar apparatus with two intercommunicating chambers. He added a compression rubber bulb to the reservoir chamber so as to expedite the flow whenever desired.

Barouse (78), in the same year, offered a model with some refinements. Its main feature is an "aspiration chamber," very useful for initial inductions. This chamber communicates with the delivery tube and is closed by a sensitive membrane which has attached at its centre a small metal disc, bearing a needle and lever system. A deflection of the pointer marks the piercing of the parietal pleura. The whole system is operated by means of a dial and pointer which permits three different communications:

1. Chest—aspiration chamber
2. Chest—manometer
3. Chest—gas chamber

Gilmour (79), in 1937, presented an instrument in which the two chambers are mounted on reciprocating arms controlled by friction disks that constitute the valve. When the fluid has passed from one chamber to the other, the position of the bottles is reversed and the apparatus refilled. If, however, the delivery tube is shifted alternately from one to the other chamber, a continuous reversal apparatus can be obtained. A two-manometer system of the Perry Morgan type is used.

The Rubin model (80) in 1937 is similar to that of Robinson, and that of Matheja (81) is no different from the ordinary hydrostatic variety.

Koch (82), in 1938, offered a machine consisting of two chambers connected end to end, one above the other. The top one is the liquid reservoir, and when the liquid has gravitated into the lower chamber and displaced all the air therefrom, it is pumped back into the reservoir by means of a rubber bulb. Of interest is the control dial and manometer system. The first permits of four settings which establish connections in such a manner that each position is respectively for:

1. Filling the apparatus
2. Injecting air into the pleural space
3. Pressure readings
4. Aspirating from the pleural space

The manometer system consists of a mercury and a water manometer connected in parallel. The mercury manometer can be set for a predetermined pressure so that when such a pressure is reached in the pleural space a bell rings to warn the operator of the event.

BELLOWS TYPE

Forlanini's original apparatus and all its later modifications belong to this group. In 1906, he added a slight improvement (86) by placing a constriction in the middle of the gasometric chamber. This enabled him to detect more readily the initial rise of fluid level when the parietal pleura was pierced and air was sucked into the chest. The rise in the fluid level was appreciable even when minimal quantities of gas left the point of the needle. This, in the author's opinion, was of the greatest importance during initial inductions. A later modification (86, 87) (figure 2b) however, in 1910, abandoned this innovation in favor, apparently, of an external water manometer which was graduated for ordinary positive and negative pressures as well as for high positive pressures. It might be added, for the sake of completeness, that this model had the usual three-way stopcock which made connections as follows:

1. Pleura—gas chamber
2. Pleura—manometer
3. Gas chamber—source of gas

Forlanini's last model (88) came in 1914, when he described his so-called "universal purpose apparatus." He simply inserted better stopcocks, both at the top of the gas chamber and at the bottom of the liquid reservoir, so that the apparatus could be used not alone for air insufflation but also for draining pleural effusions with the aid, of course, of a drain bottle.

We have already mentioned Saugman's (14) modification of Forlanini's apparatus.

In 1909, von Muralt (89) modified Saugman's instrument and discarded the mercury manometer, maintaining that the water manometer was adequate.

Lillingston (90), in England, used a simple bellows apparatus consisting of the usual two fixed bottles and a rubber insufflator.

Breccia (91), in 1913, presented a model (figure 6) which was compact and slightly new in conception. He placed the two chambers, one within the other, the outer one containing liquid and the inner one gas. He retained all the other features of the Forlanini principle. He used a Potain suction-compression pump so that the instrument served the dual purpose of insufflation and deflation. In the following year, he offered a refinement (92): more stopcocks were added so that the apparatus could be inverted without disturbing the relative position of the gas and the liquid and made it suitable for transportation. He changed back to the Richardson type of bulb for compression, while for suction and drainage of effusions, he provided an extra nozzle which could be attached to a regular drain bottle and thrown into action by one of the stopcocks. As late as 1923, he offered a third model (93) and this time he

took the two chambers of Forlanini and connected them by means of rubber tubing, converting this into a hydrostatic type. He also separated the three-way stopcocks from their respective chambers and inserted them through rubber stoppers, making them less apt to break.

Knopf (94), in this country in 1914, produced a minor modification of the Forlanini-von Muralt type, giving due credit to the original inventors. He simply included a copper coil midway in the delivery tube which he heated with an alcohol flame. This warmed the gas to body temperature.

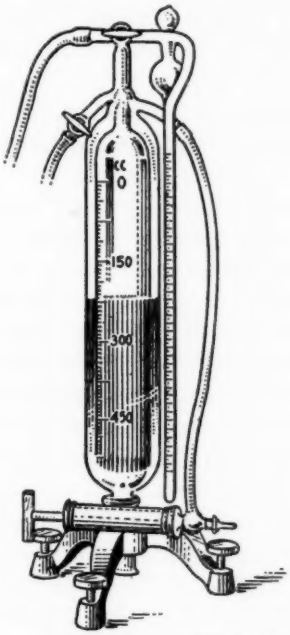

Fig. 6 BRECCIA

Kornmann's instrument (95, 96) appeared in 1914, and though it offered nothing new in principle, it had features of interest. It incorporates chambers for the chemical production of oxygen and nitrogen.[22] Nitrogen is produced by deoxygenating air as this is bubbled through a solution of pyrogallic acid and potassium hydroxide; oxygen is synthetically produced in a second chamber containing a solution of hydrogen peroxide, sulphuric acid and potassium permanganate. He claimed that gases so produced have an advantage over those taken from the commercial cylinders in being chemically, bacterio-

[22] Kornmann states that all workers before him used nitrogen from commercial tanks, but it will be recalled that Forlanini, in his first apparatus, similarly produced nitrogen in *statu nascendi*.

logically and physically pure. One or the other of the gases is switched in by means of appropriate stopcocks. Oxygen was employed for initial inductions only, in the belief that this gas was less apt to cause fatal embolism. Another feature of note is the use of a small mercury manometer connected directly to the needle; this, Kornmann claimed, made for greater sensitivity and quicker registration of the pleural pressures.[23]

Billon (98), in 1914, described a model in which he interposed two small jars with a solution of "gomenol" between the gas chamber and the needle. The gas bubbles through the antiseptic solution before passing into the chest. Billon claimed that the gas charged with the fumes of this antiseptic is not toxic and that, on the contrary, it seems to help in resolving pleuritic inflammations.

Bonnamour (62) some years later, the reader will recall, similarly used antiseptic vapors and pointed out that the incidence of pleural effusions is thereby lowered.

Müller (99) recently described what he termed "medicothorax," a new form of artificial pneumothorax with which he hoped to achieve *sterilisatio magna* of the lung, as well as the mechanical collapse of the organ. Instead of ordinary air, he used air saturated with antiseptic vapors. He employed an electro-inhalator to vaporize certain antiseptic drugs[24] and led the vapor to the air chamber of the pneumothorax machine. The author claims that his method promotes quicker healing and prompt symptomatic improvement. He states that pleural effusions are almost entirely avoided and offers this as proof that sterilization of the pleural cavity actually takes place.

Mainini (100), in 1916, presented a neat, compact and sturdy machine, based on the principle of two concentric cylinders, not unlike that previously described by Breccia. It is of superior construction and is simple to manipulate by means of a single stopcock. Two water manometers are provided, one of which reads up to 30 cm. and a second for higher positive pressures.

Henius (101, 102), in 1919, used the two chambers, connected neck to neck, one above the other. The liquid flask is the lower one, contrary to what we have seen so far, and air is displaced from the upper chamber by raising the liquid into it with the aid of bellows. To deflate, on the other hand, the liquid is simply allowed to gravitate from the upper into the lower chamber.

Frey (103), in 1920, offered a two-bottle apparatus of the familiar type. He used both oxygen and nitrogen which he derived from tanks situated behind the instrument.[25] The desired gas is admitted into the gas chamber on the

[23] Würtzen (97) in 1913 proposed the addition of a small water manometer directly to the needle, to facilitate initial inductions.

[24] Müller used a mixture of trypaflavine, camphor, menthol, oil of eucalyptus and thymol.

[25] Frey erroneously states that he was the first to use nitrogen and oxygen, but we have seen that several workers before had used both of these gases.

foreside, and then water is forced into this from the liquid reservoir. The opportune connections are made by means of the familiar stopcocks. In the following year, Frey described another type (104) in which he employed filtered air. This apparatus features two bellows. The second is used to refill the instrument by forcing the fluid back from the gas chamber into the liquid reservoir.

Lubojacky (105), in 1921, described a rather elaborate apparatus which had four chambers. Two of these, situated on the hind side, are liquid reservoirs containing a solution of sublimate and are connected with each other. The other two, situated on the foreside, are gasometric chambers, one for oxygen and the other for nitrogen, each being connected with the liquid reservoirs, manometer and delivery tube and filter. A small metal hand pump is used to force the liquid from the reservoirs into the gas chambers, while these are refilled by connecting them to gas tanks and allowing the liquid to be forced back into the reservoirs. A stopcock is provided for converting the instrument for aspiration purposes.

Samson (106), in 1922, attached a small rubber balloon to the delivery tube of his apparatus and claimed that it helped in detecting the moment when the needle enters the pleural space.

Zobel (107) used an ordinary enema syringe as an improvised reservoir to force water into a gasometric chamber.

Amandrut (108), in 1923, used a rubber bulb on the standard two-chamber type. This bulb, however, could produce pressure and suction as desired. He also added a metal manometer of the aneroid variety in the gas chamber and alleged that this registered the mean intrapleural pressure.

Newman (109), in 1926, described an apparatus of the bellows type having a special needle which provides direct communication with the water manometer. The machine is operated by means of two stopcocks fitted on this special needle. These are the only taps present and they are so arranged that no flow of air can take place except when the manometer is connected.

Weiss (110), in order to obviate the present necessity of stopping the operation for refilling, made an instrument of the bellows type with flasks of two-litre capacity.

Zimmerli (111), in 1930, modified the Forlanini-von Muralt type. He pointed out that the necessity of interrupting air insufflation each time 500 cc. of air had been used was a great inconvenience. It will be remembered that Frey endeavored to make this process of refilling easier by adding a second bellows to the gas chamber. Zimmerli, on the other hand, merely added tubing and a stopcock, connecting the single bellows to both chambers so that in one position of this tap the liquid is driven into the gas chamber—insufflation—and in the reverse position, the fluid is driven back into the liquid reservoir, thus refilling the instrument.

Abbott (112), in the same year, described an instrument similar to the Breccia-Mainini types, and termed it "a modified Murphy pneumothorax apparatus."

Joannides (113) used a Potain pump, first as a bellows to drive fluid from the reservoir to the gas chamber, and then as an aspirator to suck it back into the reservoir, thus refilling the instrument. It also served to drain pleural exudates.

Galmozzi (114), in 1931, added to the Forlanini apparatus another glass chamber and placed it before the delivery tube. This is immersed in a tank of hot water to warm the gas before it enters the chest.

Hunt (115), in the same year, described an apparatus essentially the same as all the others of this type. He simply shifted the bellows from one chamber to the other to refill the apparatus.

Birkinshaw (116) used a compressed gas tank to force the fluid from one chamber to the second.

In 1932, Singer (117) described a compact apparatus consisting of two chambers connected neck to neck vertically. Paraffin oil is used as the fluid medium and this is forced from the lower to the upper chamber by means of a bellows. When it gravitates back into the lower chamber, air is driven into the chest. A new type of manometer is used, consisting essentially of an elastic rubber bulb, mounted in a metal case: when it is connected to the delivery tube, the bulb dilates or contracts in accordance with the variations of the intrapleural pressure, these variations being recorded on a scale. A single commutator valve controls the operation of the apparatus and permits air insufflation, deflation and pressure readings. The valve is operated by a lever and dial.

Slabodyonick (118), in 1936, described a model of the Henius variety.

INDUSTRY'S PRACTICE IN THE EMPLOYMENT OF EX-PATIENTS[1]

EDWARD HOCHHAUSER[2]

Can I get my job back again if I develop tuberculosis?

The answer does not depend upon the type of industry or even its size, but upon the attitude, the intelligence and the experience of my employer.

If I work for the XY Railway Company in the Middle West, I am fired the minute a diagnosis of tuberculosis is made and never will be reëmployed. If I work for the AB Railway Company I will receive hospital care and am assured of a job when the doctor finds me able to return to work.

At one meat packing plant with over 5,000 workers, I can never get back on the job if I have tuberculosis, while at another equally large plant I may be reëmployed, but assigned to a job where there is no danger to customers or to myself. If I happened to be employed by one large shoe company, not only do I receive medical care free, but when I leave the sanatorium I return to a part time job which is slowly increased to a full day.

Why is industry's attitude so important? Because during the working age between eighteen and thirty-five tuberculosis is in first place as the cause of death. This, in spite of the fact that deaths from tuberculosis have decreased until they are less than one-quarter as many as thirty years ago. Industry may not be responsible for the high incidence of tuberculosis during the working age, but it can play a large part in the rehabilitation of these men and women. Whether it does this because of a philanthropic impulse—or in recognition of its responsibility as employers—or because it pays, matters little. A large number of employers are doing an excellent job in returning the tuberculous workers to a normal working life, while others are indifferent or worse.

The Metropolitan Life Insurance Company has demonstrated that an intelligent scheme of medical examination can reduce the number of cases of tuberculosis, but what is equally important, they are finding more patients in the early stages of the disease.

[1] Read at the Conference of the New Jersey Tuberculosis League, Asbury Park, New Jersey, June 2, 1939.

[2] 71 West 47th Street, New York City.

In 1928, 76 per cent of their employees found to have tuberculosis were in the advanced stage of the disease, and only 24 per cent in the early or minimal stage. In 1937, only 10 per cent were advanced cases and 90 per cent minimal cases.

Among the Metropolitan employees observed were 2,700 who were X-rayed over a period of ten years. There were some arrested cases of tuberculosis with calcified lesions. In the ten-year period more cases of active tuberculosis developed among the well workers than among the "arrested" cases.

The medical director of a large tobacco company wrote me:

> In two surveys we have taken 1,000 X-ray plates of presumably healthy employees. Cases of arrested tuberculosis found were twice as frequent as the active cases found. All these cases of arrested tuberculosis were kept at work and under observation. Only three out of 23 have subsequently broken down.

How unfair and scientifically incorrect it would have been to refuse to continue to employ these arrested cases, yet there are many employers who refuse to reëmploy a worker who develops tuberculosis even after successful treatment.

The inevitable result is that patients who should seek sanatorium treatment continue to work as long as they can with active disease, minimizing their chances of getting well again, and continue a potential danger to those around them. They cannot observe the precautions that might make them reasonably safe for fear that their tuberculosis might be suspected. This is particularly true in the one-industry community.

A state agency in one of our mid-western states found a number of advanced, open cases of tuberculosis working in the assembling department of one such industry even though sanatorium treatment had been recommended and the state was ready to provide adequate treatment. On inquiry it developed that if the management learned that an employee had tuberculosis he was fired and it was known that he would never be reëmployed. As the employer had no program of medical examination, he did not know of the presence of tuberculosis.

Is industry indifferent to its tuberculous employees? Are the companies that have a well planned scheme of reëmployment prompted by a philanthropic impulse; are they prompted by an economic interest and have they found that it pays?

Industry's attitude has a far reaching effect.

On finding the worker with tuberculosis in the early stages, when the chance for getting well is fairly good;
On his continuing to take treatment until he is able to return to work;
And, most important for the individual patient, on his chances of rehabilitation and a normal life.

We know of 203 employers with over 1,600,000 employees who reemploy workers with arrested tuberculosis under schemes that run from indifference to complete medical and industrial supervision, while some of these employers with over 630,000 workers provide part-time work for patients who, on leaving the hospital or sanatorium, are not able to work a full day. One large shoe company with over 19,000 workers has reëmployed approximately 200 tuberculous patients over a period of years. Since they inaugurated a scheme of part-time work on initial reëmployment until recovery is complete, the instance of renewed disease has been comparatively rare.

There is very meagre information on what industry does for its tuberculous workers—whether it would give a job to a new worker who had tuberculosis. There was still less before we started our inquiry in preparation for a study on the industrial aspects of the rehabilitation problem of the tuberculous.

We knew of the experience of sheltered workshops and industrial colonies for the tuberculous in this country and abroad. They had demonstrated that relapses—breakdown after successful treatment—can be reduced and patients in all stages of the disease gradually returned to work and partial or complete self-support. The Altro Work Shops in New York City have provided industrial convalescence for the tuberculous for twenty-four years. Their experience with approximately 1,000 patients has demonstrated what can be done in bridging the gap between sanatorium treatment and a normal life.

In getting well we have made considerable progress; not so in staying well, or in the return to the job. The rehabilitation of the tuberculous has until recently been a neglected phase of the tuberculosis program. The 50,000 tuberculous patients who leave hospitals each year with their disease improved are interested in their chances of staying well and getting jobs. The community has spent from $200.00 to $4,000.00 for each patient's treatment.

The more effective our treatment for tuberculosis, the more patients will survive. Those who survive must be permanently institutionalized or we must give them an opportunity to work in accord with their physi-

cal ability, their skills or their adaptability translated through vocational rehabilitation into new skills.

The only adequate treatment for unemployment for the tuberculous is a job—sheltered work if the patient is not physically ready for normal work; if able to work a normal day, a job at made work (work relief) but better still, a job in industry.

Sheltered workshops will be needed to care for many patients, and to serve as demonstrations of what can be done in returning patients to normal industrial life.

Work relief is better than home relief for employable men and women who are in need, but at best it is unsatisfactory. With the wisest of planning and supervision, work relief seems to have by-products that are bad for the community and for the individual.

Sheltered workshops are better and cheaper than indifference, neglect or relief without any plan for rehabilitation. But, as with all charitable activities, workshops carry with them a danger to the morale, to the very spirit they try to create or preserve, that does not go with a job in industry.

Returning to a job after successful treatment or to a readjusted job with his old employer has many advantages for the patient. It also has many advantages for the employer. It pays both as truly as in neglect they both pay. It is good personnel practice and makes for a better morale if it is known that a worker who develops tuberculosis and is treated successfully has a job waiting for him when the doctor finds him ready to work. The possibility of a job is good therapy for the patient at the sanatorium and assures an adequate stay, for his job depends upon recovery.

Making tuberculosis a compensable disease has obvious advantages for the individual whose disease may become a charge on industry. But a scheme of pensions or disability allowance that is not tied up with treatment, rehabilitation and employment is not sound and puts a premium on invalidism. One could not achieve, through a pension, the same medical or social results that could be obtained through the provision of work.

As compensation laws increasingly include tuberculosis, it becomes more important to the employer to coöperate in a scheme of reëmployment.

We know of the temptation to nourish a handicap when it is to our financial interest to continue disabled. A patient who applied for

admission to the Altro Work Shops later decided it was not to his interest to be rehabilitated. An insurance policy with a disability clause had paid him $125.00 since his illness. He was found in need of carefully graduated work, should start at not more than three hours and within two years might be able to work a normal day. But then his income would cease. He preferred his disability and $125.00 a month.

While willing to reëmploy their own workers who develop tuberculosis and cure successfully, we found many concerns will not accept a similar patient for initial employment. The medical supervisor of an automobile company employing 3,000 said:

> We do not discriminate against persons previously in our employ who have contracted tuberculosis and subsequently became arrested and able to work. We give considerable thought to placement of such individuals. I cannot give you figures as to how many we have had in the past fifteen years, but we have had our share and we have attempted to rehabilitate our own cases. We object, however, to take on the load from somebody else.

We frequently hear that industry would be willing to reëmploy their tuberculous employees when able to work if it were not for the attitude of insurance carriers.

"As far as I know no insurance company has expressed any attitude either for or against reëmployment of arrested cases of tuberculosis" wrote one company which has been reëmploying their own tuberculous workers over a period of twenty years with an excellent program of medical care and supervision.

The surgical director of another nationally known company wrote:

> You have heard contradictory opinions as to the attitude of insurance companies, relative to whether they believe it is wise to reëmploy arrested cases of tuberculosis. Of course, I can speak only for the Liability Division of my own organization, relative to workmen covered under compensation insurance policies, but from my conversations with representatives of other carriers, I believe their attitude is essentially the same as ours.
>
> You agree that there are instances where this may not be wisely done. For example, the arrested case of tuberculosis whose previous employment involved unusual conditions such as extremes of temperatures, exposure to irritating gases, or work under high pressure probably should seek employment of a different character for their own safety. In fact, as you will agree, the attending doctor would perhaps object to reëmployment under conditions of such character. However, except in instances of this type, I seriously doubt if insurance carriers object to reëmployment, and in fact, from our own ex-

perience, it is urged. In practice, if a patient is able to resume duty, after active tuberculosis, it would be difficult to obtain release from the payment of compensation if employment were denied at the previous occupation, unless some other employment were discovered. It is ordinarily a great deal easier to return a patient to work, with perhaps some opportunity to permit him a period of rehabilitation when he is not expected to do as well as before, through the previous employer. To ask someone else to take the patient, be somewhat easy on him or her until they became reaccustomed to their new duties, is most difficult indeed in actual practice. Therefore, I believe the vast majority of those who are ready to resume duties return to their previous employment, we take no exception to their doing so except in obviously unusual circumstances, and I doubt if other insurance carriers proceed indifferently. There would be no good medical reason for their so doing, and objection to reëmployment would in general increase costs under compensation insurance. Of course many employers take an attitude one way and others differ. This is probably largely due to their own individual experience in a few cases, or to the personal feelings of their executives toward the disease. I feel certain that those who have given the subject scientific consideration believe that it is safe from a medical viewpoint to reëmploy arrested cases except in unusual conditions and philanthropically wise.

Since this entire subject is one that is controversial indeed, one to which I doubt if it would be proper for us to become an active party, I would therefore request that you keep my opinion expressed herein as personal and confidential.

We inquired whether the fact that workers who develop tuberculosis might be reëmployed was known to employees, and whether the fact aided in earlier diagnosis. Of the 78 companies who replied, 57 believed this knowledge had some influence, 4 were doubtful and 17 stated it had no effect. The medical director of an oil company wrote:

There is no doubt that the knowledge that employees will be cared for does encourage them to report for early examinations if they feel below par. You may be interested to know that in recent years the pulmonary tuberculosis rate among company employees is exceedingly low. During the year 1937, among a group of 32,262 employees, there were only eleven new cases, which is a frequency rate of .34 per 1000 per annum. This compares with a frequency rate of .8 per 1000 as reported by the United States Public Health Service for a group of 185,000 industrial employees.

With regard to the loss of time of these reëmployed arrested cases as compared with all other employees there was considerable testimony. Ninety-seven replied, 87 stating that in attendance the reëmployed

tuberculous compared favorably or were better, five reported they were less favorable, and five stated that their loss of time was slightly higher.

From the personnel director of a bank employing about 6,000:

The attendance records of the recovered cases who have returned to work I know with exactness are as good if not better than others. We exercise constant supervision and have them reëxamined frequently for a full year after return. Furthermore, having come through this experience, they pay stricter attention to their health problems and use more caution and care about diet, rest, exercise, etc. Our experience with these people both in the matter of treatment and their control after return has been most gratifying.

From the medical director of a company employing over 46,000:

We have had twenty years of experience reëmploying our tuberculous workers. We are quite happy with our results. As for the question of attendance records of these recovered cases, we made a check up a few years ago and found, as we have on previous occasions, that the average attendance record of the recovered tuberculous group as related to sickness absence was better than the average of the whole body of employees.

The number or percentage of relapses reported were in most instances estimates. A number spoke of the importance of medical follow-up. One personnel director wrote:

From our own experience would say that the method for prevention of breakdown after return to work lies in carefully following out of instructions given by the physician, who is a competent chest expert, and continued periodic check up as specified by him. We have always carried out the policy, which I believe, with good coöperation of the employee, accounts for the good results we have had with our tuberculous cases.

The chief physician of a company employing 4,300, which has reemployed about 50 tuberculous workers and reports very few relapses, wrote:

Employees with arrested tuberculosis are kept under our hospital observation, reporting for a periodic examination by our physician, which is a preventative against breakdown.

The medical director of a steel company with 50,000 workers wrote, "Relapses occur unless carefully checked."

A railway company employing 25,000 stated, "If classification of employment is accurately gauged, relapses are infrequent."

Dr. Ronald E. Lane in the December, 1937 Tubercle reported on a study based on answers from 24 whole-time medical officers in industry.

One of the larger organizations has an excellent scheme whereby all light jobs are scheduled . . . when cases requiring light work occur, a list of suitable openings is available . . .

My own personal experience has been a happy one, and although my numbers are very small (32 cases) over 60 per cent of all my tuberculous cases are still at work, two-thirds of these having survived five years and being now on full productive work. I would emphasize, moreover, that my experience is not confined to one large factory, but is based upon a number of small units—some of less than 100 employees. It is perhaps, therefore, of more interest than if it were limited to one large unit.

One hundred and eighteen companies reported on relapses, although often in generalities rather than specific figures or percentages. If we add together all who reported no relapses, relapses rare, satisfactory and from 10 per cent to 20 per cent, we have a total of 90, or 76 per cent of the number who replied. Those who reported relapses as frequent and from 22 per cent to 50 per cent number 25, or 21 per cent of the 118.

I sent copies of my study to the 219 industrial organizations who assisted me. In summarizing my observations I suggested that, whether from public or private funds, as philanthropy or insurance, disability allowances or pensions that are not concerned with rehabilitation and reëmployment are not sound and put a premium on invalidism.

That the possibility of a job is good therapy for the patient at the sanatorium and assures adequate stay, for his job depends upon recovery.

That the time is ripe for stimulation and education of industry and for exchanging experiences.

The medical director of one of the largest department stores in the United States, in acknowledging my study, wrote in part, "I thoroughly agree that every attempt should be made to get these people back to their former occupation. Our own experience has been very favorable with these people and relapses very few."

The personnel director of a large insurance company wrote, "Publicity along this line should be helpful to the tuberculous as well as to the companies in determining their attitude towards arrested cases."

The comment of the Director of Industrial Relations of a large machine manufacturing company was most interesting, "I believe that a special effort should be made to sell the idea of employing handicapped people to the workmen themselves. It is my impression that most progressive managements will coöperate if they have not to fear prejudices on behalf of their employees."

TUBERCULOSIS SURVEY IN VERMONT[1]

LOUIS RABINOWITZ, EDWARD J. ROGERS AND HAROLD W. SLOCUM

As in other states, the tuberculosis control program of Vermont is divided into two divisions. One consists of finding new cases of tuberculosis, and the other includes the broad field of supervising the treatment and after-care of tuberculosis patients.

A study of tuberculosis mortality in the United States by counties leaves one to conclude that the mortality rates are in no way modified by whether a population is rural or urban, or whether the section is mountainous or in a valley (1). The high point of mortality in the East appears to be in Kentucky and Tennessee, while a lower zone extends along the Atlantic coast from Maryland to Maine up along the Hudson River through New York State and most of New England.

Vermont and the other New England states have shown a decided decline in tuberculosis mortality within the last decade. The average Vermont tuberculosis mortality for the five-year period, 1925 to 1929, was 72.3 per 100,000. It dropped to 46.4 per 100,000 for an equal period ending in 1937.

This steady decline in the tuberculosis death rate in Vermont has been parallel to that noted in the United States as a whole. This decline has been a definite one when compared with the causes of all deaths. Whereas, in Vermont, 4.6 per cent of all deaths were due to tuberculosis of the lungs in 1928, 2.9 per cent represented the same cause in the year 1935.

Upon studying the average tuberculosis death rate in Vermont by counties we note that it has tended to remain unusually high in certain sections of the state (table 1).

Washington county has had a tuberculosis mortality of almost five times that of the remainder of the state. Excluding this county, the mortality for the remainder of the state averaged 34 per 100,000.

Washington county is the centre of the granite industry in the state

[1] From the Vermont Sanatorium, Pittsford, Vermont, Vermont Department of Public Health and the University of Vermont Medical School, Burlington, Vermont.

of Vermont. Routine X-ray examinations of the workers in this industry have shown the prevalence of silicosis and a high incidence of infection.

TABLE 1

The annual average death rate from tuberculosis per 100,000 population by counties in Vermont

COUNTIES	1925–1929	1934–1937
Washington	206	154
Windham	70	42
Rutland	69	54
Chittenden	66	41
Franklin	62	30
Caledonia	58	42
Addison	57	13
Orange	49	34
Lamoille	47	34
Bennington	42	22
Grand Isle	40	13
Orleans	36	26
Windsor	35	22
Essex	22	33

TABLE 2

Estimated cases of active tuberculosis in Vermont by counties for each year (1934–1937)

COUNTY	POPULATION (1938)	ACTIVE CASES EACH YEAR
Washington	41,732	553
Rutland	48,441	233
Windham	25,015	95
Caledonia	27,232	102
Chittenden	47,376	173
Orange	16,690	33
Lamoille	10,945	34
Franklin	29,928	81
Addison	17,945	21
Bennington	21,671	44
Grand Isle	3,940	5
Orleans	23,076	54
Windsor	37,416	73
Essex	7,144	27
Total	359,611	1,529

On the basis of the Framingham formula of 9 active cases of tuberculosis to each annual death, table 2 suggested the task of finding these cases and the counties where they were most apt to be found.

The question, at first, concerned itself about the groups of people to be studied. We knew the areas where the disease was most likely to be found. We needed more information as to the ages of the individuals to be studied in these areas.

Consequently, our next step was to determine the prevalence of tuberculous infection in the preadolescent children in the state of Vermont. We did not have the facilities for examining very large groups of such children, and so we had recourse to sampling studies. In all there were 1,050 children examined between the ages of five and twelve years. Most of them were studied at the Caverly Preventorium in Pittsford and the Free Dispensary Pulmonary Clinic of the University of Vermont Medical School in Burlington. These children were drawn from all parts of the state and represented the lower economic strata. They were equally divided as to sex.

TABLE 3

Tuberculin and X-ray study of 1,050 children in Vermont, five to twelve years of age

TUBERCULIN REACTION (0.1 MG. OT)	CONTACT PRESENT	CONTACT ABSENT	REINFECTION PULMONARY TUBERCULOSIS	PER CENT OF TOTAL
	per cent	*per cent*		
Positive	12	18	0	30
Negative	4	66	0	70
Total	16	84	0	100

As can be seen from table 3, 30 per cent had a positive Mantoux reaction. The study suggested that tuberculous contact markedly increased the number of children, under twelve years of age, with tuberculous infection as evidenced by the tuberculin test.

X-ray examination of all the children, positive and negative reactors, disclosed no evidence of reinfection pulmonary tuberculosis. A similar study in New York City disclosed only 2 cases of reinfection tuberculosis in 963 children X-rayed (6).

From this study we concluded that the investigation of groups of preadolescent children would not yield enough cases of pulmonary tuberculosis to justify the great expenditure necessary. It was decided to examine in regular pulmonary clinics those children who were in direct contact with open cases of pulmonary tuberculosis, or who presented respiratory symptoms, but not to expend any of our facilities in any group surveys of preadolescent children.

Since all morbidity and mortality rates show a steep rise in pulmonary

tuberculosis in adolescence, we next decided to survey this group in the state of Vermont. Thereupon, consent applications were given out to the parents and guardians of young people in most of the high schools and a few grade and normal schools in the state. Tuberculin tests were performed and the positive reactors were X-rayed.

Out of a total school population of 10,311 adolescent individuals, 5,065, or about 50 per cent of the entire group, were given the tuberculin test.

TABLE 4

Tuberculin survey of school children in the state of Vermont by counties

COUNTY	NUMBER OF CHILDREN TESTED IN AGE GROUPS (YEARS)				PER CENT POSITIVE
	5-9	10-14	15-19	20+	
Bennington	0	97	65	1	43
Chittenden	0	44	51	0	37
Washington	7	398	626	5	32
Franklin	55	358	363	1	29
Rutland	58	216	401	61	25
Windham	41	273	197	2	25
Addison	29	98	99	1	23
Lamoille	69	151	132	24	22
Caledonia	0	61	320	58	21
Windsor	16	311	440	4	19

TABLE 5

Tuberculin reactions in children of high school age

STATE	YEAR	AGE GROUP	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
		years			
Vermont	1937	10–19	5,065	1,294	26
Rural Pennsylvania (2)	1936	10–19	10,358	2,250	22
Rural Michigan (3)	1935	10–19	4,202	842	20
Cattaraugus, New York (4)	1933	13–19	705	111	16

The ages averaged between ten and nineteen years. The number of children reacting positively to the Mantoux test (0.1 mg. OT) was 1,294, about 26 per cent of all the children tested (table 4).

As can be seen from similar studies in sections of the country like Vermont the incidence of tuberculosis, as evidenced by the tuberculin test, is not much different (table 5).

All these young people with positive tuberculin tests were examined by X-ray. Five were found to have active reinfection pulmonary tuber-

culosis. These constituted 0.4 per cent of the total number given the tuberculin test.

A comparison of the latter findings with studies by other investigators revealed no appreciable difference (table 6).

Although this study did not reveal any great amount of pulmonary tuberculosis, the educational value was large. The necessity of the X-ray examination in the search for early cases of pulmonary tuberculosis impressed itself upon the minds of the students and their parents.

The next step in the search for early pulmonary tuberculosis resolved itself around the question of the possible source of the tuberculous infection in the children studied.

In order to obtain this information 688 children with positive tuberculin reactions were followed back to their homes and other surroundings. There were 54 entire families studied as a result of this effort. The entire

TABLE 6

Results of examination by X-ray of high school children

STATE	YEAR	METHOD	AGE GROUP	TOTAL EXAMINED	POSITIVE TUBERCULIN	TOTAL X-RAY	REINFECTION LESIONS
			years				
Vermont	1937	1 film	10–19	5,065	1,294	1,294	5 (0.4%)
Pennsylvania (2)	1936	1 film	10–19	10,358	2,250	950	5 (0.1%)
North Carolina (5)	1935	1 film	13–20	3,235	522	407	6 (0.2%)
New York (6)	1938					6,325	24 (0.4%)

investigation yielded 591 adults as possible sources of tuberculous infection.

All these individuals were studied by X-ray. We found 17, or 3 per cent of the total number, with active pulmonary tuberculosis.

An almost similar study in Kingston, New York, revealed about the same findings (7).

This decided increase in the number of cases of active pulmonary tuberculosis found by X-ray survey of contact sources in adults suggested one method of finding people ill with this disease.

The next question we had to answer was how we could find pulmonary tuberculosis in its earliest stage of development. A review of the patients entering the Vermont Sanatorium in Pittsford through a ten-year period showed fewer than 5 per cent with the disease in the minimal stage.

In an attempt to find the patients with the disease in the earliest stage

when its treatment is most effectual, Consultation Pulmonary Clinics were organized by the Division of Tuberculosis of the Vermont Department of Public Health in coöperation with the Vermont Tuberculosis Association. These have been held in all parts of the state at regular intervals. Patients are studied in these clinics upon request of their own physicians. The complete examination has consisted of a history, tuberculin and sputum examinations when indicated, and physical and X-ray examinations of all chests. A report has been rendered to the physician referring the case.

From a study of 2,400 consecutive patients referred to these Pulmonary Clinics by general practitioners, 11 per cent of those examined were found to have reinfection pulmonary tuberculosis. These findings were somewhat higher than similar studies in New York City where examinations of 50,000 individuals revealed 7.6 per cent with tuberculosis (6).

Of the 355 cases of pulmonary tuberculosis found in this group of 2,400 people, 204 were found to be active and required immediate medical and sanatorium treatment.

But the most significant result of this investigation was that 111, or more than 50 per cent of this group with active pulmonary tuberculosis, had the disease in the minimal stage.

This was decidedly different than the number of patients with the disease in the minimal stage entering the sanatoria. The latter group constituted less than one-twentieth of the total number entering the institutions.

A recent similar tuberculosis survey in Florida disclosed 77.8 per cent of the reinfection cases in the minimal stage (8).

Unquestionably, the first line of attack in finding pulmonary tuberculosis in the early stage, when its treatment is most efficient and most economical to the community as a whole, depends upon the physician in general practice. How can he be helped most efficiently to find these cases?

Since the history has always been considered to be of value in the examination of the patient, we analyzed the histories of the 355 cases of pulmonary tuberculosis as to contact, haemoptysis and symptoms of pleurisy.

Over two-thirds of the patients gave a story of contact with pulmonary tuberculosis. A history of pleurisy was present in about one-fifth of all the cases. The presence of haemoptysis was detected in 7 per cent of the minimal cases and 40 per cent of the advanced cases. Its absence

did not seem to be of much value in helping us find the disease in the early stage.

Again the question came up as to the value of the stethoscope in finding reinfection tuberculosis. The physical examination findings of the 355 cases were again analyzed as to the presence of crepitant and bubbling râles extending anywhere from the apices to the third rib in front or the fourth dorsal vertebra in back, as well as the usual findings in cavity cases, such as bronchial sounds, bronchophony and pectoriloquy.

We found auscultatory signs in about nine-tenths of the advanced cases, and in only two-tenths of the minimal cases. We could find nothing with the stethoscope in four-fifths of the minimal cases. Cavity signs were present in one-tenth of the chests with advanced disease. It would seem, from this study, that very few of the minimal cases of pulmonary tuberculosis could be found by physical signs.

As was expected, the frequency with which tubercle bacilli were found in the sputa increased as the disease process advanced. They were found by direct smear in 14 per cent of the minimal, and 66 per cent of the advanced cases.

From this study we concluded that a history of contact with active pulmonary tuberculosis was significant inasmuch as it frequently brought to the physician, for study, minimal cases of pulmonary tuberculosis.

We also concluded that a history of haemoptysis and pleurisy was most frequently absent in the disease at this early stage.

We found that the absence of physical signs was of no significance in eliminating the existence of the disease.

Similar studies by Kallner (9) in 605 cases showed 81 per cent with no history of pleurisy. Maxwell (10) found 75 per cent of 340 cases with a similar story. Sampson and Brown (11) reported 88 per cent of 280 minimal cases with no history of effusion. Fellows (12) found 65 per cent of 141 cases with no pathognomonic symptoms.

Chadwick (13) reported 440 cases with no auscultatory signs in 79. Mark (14) found 50 per cent of 41 cavity cases with no signs. Sampson and Brown (11) reported no râles in 73 per cent of 280 minimal cases.

CONCLUSIONS

From this study it would seem that an effective method for finding pulmonary tuberculosis in the earliest stages would be to examine by X-ray the chest of any adolescent or adult who has had contact with pulmonary tuberculosis, such as relatives, friends and nurses of patients.

All employees in dusty industries, such as granite and slate, should be routinely examined. All teachers, normal school students and members of families where children board should have their chests studied at least once. All house servants where children live should be examined in a similar manner.

All patients entering any hospital for any reason should have their chests X-rayed routinely.

Any person with respiratory symptoms, such as "grippe" and persistent cough present more than two weeks or of frequent occurrence, should be examined by X-ray. No lung can be called healthy without an X-ray examination.

In the state of Vermont, the individuals who may possibly have pulmonary tuberculosis are most frequently first seen by their local physicians. Since the absence of physical signs does not prove the nonexistence of the disease, consulting X-ray examination facilities should be available to help physicians in general practice determine the presence of pulmonary tuberculosis in their patients. The Health Department, Sanatorium and General Hospital Consultation Pulmonary Clinics most efficiently and economically produce this type of service and should be extended.

SUMMARY

1. A comparative study of tuberculosis mortality in Vermont by counties is presented.

2. A study of 1,050 preadolescent children drawn from all parts of Vermont disclosed no reinfection pulmonary tuberculosis.

3. A survey of 5,065 adolescent children, from a total school population of 10,311, showed tuberculous infection present in 26 per cent of the children studied, with active reinfection pulmonary tuberculosis in 0.4 per cent.

4. Another study of 591 adult contacts with 688 children having positive tuberculin reactions disclosed 17, or 3 per cent, with reinfection pulmonary tuberculosis.

5. Examinations of 2,400 individuals referred by physicians in general practice to Consultation Pulmonary Clinics revealed 11 per cent with reinfection pulmonary tuberculosis, of which number 54 per cent were in the minimal stage.

6. Further analysis of the previous examinations showed two-thirds with histories of contact, one-fifth with histories of pleurisy, less than

one-tenth of the minimal cases with histories of haemoptysis and more than four-fifths of the same group with no auscultatory signs.

7. An effective method for finding minimal pulmonary tuberculosis in the state of Vermont is suggested.

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TUBERCULOSIS IN NURSES[1]

A Seven-Year Study at Cook County Hospital

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With the assistance of Miss Dorothy L. Campbell[2]

Until 1938 the measures taken to prevent tuberculosis in nurses of the Cook County Hospital were confined chiefly to the students of the nursing school, although precautions against contagion were carried out by all nurses in the tuberculosis hospital. Preliminary to increasing the emphasis on the tuberculosis prevention program and enlarging it to include the other nursing groups of the hospital (namely, the graduates, postgraduate students and affiliates) a stock-taking of the tuberculosis among all of the nurses in the last seven years seemed desirable. The data presented here are the findings of a committee appointed for this purpose. The efficacy of the enlarged tuberculosis control program recommended by this committee can be judged by similar reports to be made on tuberculosis in the nursing group in the ensuing years.

For the past four years the students of the Cook County School of Nursing have had routine chest films at the time of their entrance and final examinations. Films were often made at the time of routine yearly physical check-ups if any suspicion of tuberculosis was aroused in the mind of the examining physician. Mantoux tests were performed at the time of entrance also. For the past two years these have been repeated at yearly intervals on those having originally negative tests, until the tests became positive. Most graduate and postgraduate nurses also had entrance and yearly physical examinations, but not chest films as a routine measure. Certificates of good physical condition were required of the home schools of all affiliating students. But because these nurses remained only several months, routine examinations or Mantoux tests were not made. All nurses were encouraged to report even very minor disabilities at the dispensary of the nurses' infirmary. Here any symp-

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toms suggesting even remotely the possibility of pulmonary tuberculosis prompted the ordering of chest films. Rapid drops noted in the monthly weight records made on all student nurses often led to the ordering of films. Probably the maximum number of cases of pulmonary tuberculosis which it is possible to discover without routine X-ray films of every member of the nursing staff were found. However, as recently pointed out by Long and Seibert, probably in four-fifths of the cases of mild tuberculosis medical consultation is not sought by the patient. They are discovered only if routine chest films are made (1).

In the years 1930 to 1937, inclusive, 52 cases were found in a group that averaged 991 nurses, an incidence of about 6 cases per 100 nurses per year. It is interesting that 10 of these cases were found within three months of the time the nurses came to Cook County Hospital; so that

TABLE 1

Distribution of clinical tuberculosis among groups

	AVERAGE NUMBER IN GROUP	CASE INCIDENCE FOR 7-YEAR PERIOD	AVERAGE CASE INCIDENCE PER 100 NURSES PER YEAR	
Cook County School of Nursing students	111	3	0.39	
Graduate nurses*	505	17	0.48	
Postgraduate nurses	165	12	1.04	.63
Affiliates	210	10	0.68	

* Four of these graduates were Cook County School of Nursing students and developed tuberculosis within two years of their graduation.

undoubtedly the nurses were already infected at the time they went on duty. Only one had a routine physical examination and chest film on entrance to training at the hospital, and it was at this time the tuberculosis was discovered. All of the others presented satisfactory certificates of physical examination made just before they arrived. The need for chest films and examinations at the Cook County Hospital in addition to this check was thus amply demonstrated. Particularly interesting was the fact that 5 affiliate nurses, who supposedly had been under supervision at their own hospitals up to the time they came to Cook County Hospital for training, were found to have active tuberculosis.

The distribution of active tuberculosis among the various groups is shown in table 1. The lower incidence in the nursing school students is probably due to the fact that fewer of the individuals had had impor-

tant exposure to tuberculosis prior to coming to Cook County Hospital than in the other groups, and the turn-over in this group was less rapid. It will be noted that some of the nurses originally in the student group eventually developed tuberculosis after they had become graduates.

Comparison of tuberculosis in nurses of Cook County Hospital with other groups of nurses and medical students shows that the incidence is about the same (table 2). These data appear less favorable, however, when it is recalled that routine chest films were not made on every nurse regardless of symptoms, except those of the training school. The actual incidence of tuberculosis was probably higher at Cook County Hospital

TABLE 2

Comparison of incidence of tuberculosis in Cook County Hospital nurses with that in other schools of nursing and in medical students

	AVERAGE NUMBER IN GROUP PER YEAR	NUMBER OF CASES DISCOVERED	INCIDENCE PER 100 INDIVIDUALS PER YEAR
Cook County Hospital nurses			
Students	111	3 in 7 years	0.39
Graduates and affiliates	880	39 in 7 years	0.63
Bellevue Hospital nurses (2)			
Students	312	8 in 5 years	0.51
Graduates and affiliates	746	26 in 5 years	0.70
Western Reserve medical students (3)	250	11 in 8 years	9.55
Johns Hopkins medical students (3)	250	10 in 5 years	0.80
American college students (4)			
From colleges in which an active tuberculosis case-finding program was in effect	85,428		0.57
From colleges in which an active tuberculosis case-finding program was not in effect	13,000		0.12

than in Bellevue Hospital and the other institutions cited where more intensive case-finding methods were in effect.

Unfortunately up to 1938, tuberculin testing at the Cook County Hospital has been done routinely only on the student groups, and follow-up testing only for the past two years. In the relatively small group retested it is seen (table 3) that at the end of two years of training 62 per cent of those originally negative to the Mantoux test had become Mantoux positive. In the group of graduates and permanent staff nurses tested after this survey was begun, 93.4 per cent of a group numbering 778 were found to be Mantoux positive. In all likelihood tests on our own students at the end of three years will give comparable

results. At the Cook County Hospital all students and many affiliates and graduates are required to take the regular tuberculosis service of three months. There is also exposure to active cases on the medical wards, orthopedic wards, and in the children's hospital. A survey made by the medical resident revealed that during the three months of April 1,

TABLE 3

Results of Mantoux tests in Cook County Hospital nurses

	NUMBER OF TESTS	POSITIVE
		per cent
Tests on students made with Old Tuberculin soon after admission to training	209	31.0
Tests made with similar material one or two years later (not at completion of training) on students originally negative to Mantoux test	76	62.0
Tests on graduate nurses—all after three years or more of training at Cook County or other hospitals	778	93.4

Of the 42 nurses who developed clinically recognizable pulmonary tuberculosis after coming to Cook County Hospital, only 6 had Mantoux tests on entrance. Of these, 3 were positive and 3 were negative. In the latter 3 cases, the original infection was undoubtedly contracted at the hospital.

Results of Mantoux tests in other groups of nurses

	PERCENTAGE OF POSITIVES	
	On entrance	After three years training
Heimbeck (Quoted by Myers (5)) Oslo	50.0	100
Geer (Quoted by Myers (5)) Ancker Hospital, St. Paul, Minnesota	30.0	Almost 100
Myers (6):		
Hospital no. 1 having required tuberculosis service	22.8	94.33
Hospital no. 2 having only occasional tuberculosis cases	23.8	43.56
Hospital no. 3 having only occasional tuberculosis cases	23.63	35.32
Minnesota School of Education—no known contact with tuberculosis	24.8	28.5

1938 to July 1, 1938 there was an average of 30 to 40 patients with pulmonary tuberculosis in the men's medical wards. The average length of stay was fourteen days. In the female medical wards there was an average of 10 tuberculosis patients, with an average length of stay of ten days.

The incidence of positive reactors among entering students is practi-

cally identical with that in other similar age groups in the general population. In 26,861 college students tested with PPD 29.4 per cent reacted positively (Long and Seibert (4)). Myers, Geer (table 3) and others have shown that, in hospitals with required tuberculosis service, the incidence of infections as demonstrated by the Mantoux test is practically 100 per cent at the end of three years' training, somewhat lower in those hospitals where contact with tuberculosis is only occasional. In the Minnesota School of Education, among students who had no known exposure to tuberculosis, the increase in positive reactors was only 4 per cent in four years. The highly infectious nature of active

TABLE 4

Symptoms which aroused suspicion of tuberculosis on the part of the patient or the examining physician in order of their frequency—report on 52 cases

Cough	26 times
Loss of weight	24 times
Undue fatigue	24 times
Thoracic pain	24 times
Continued fever	15 times
Haemoptysis	8 times
Prolonged upper respiratory infection	7 times
Anorexia	4 times
Hoarseness	4 times
Night sweats	2 times
Amenorrhoea	1 time
Epigastric pain	1 time
Dyspnoea	1 time

In 7 instances the diagnosis was made from routine chest films; the patient had made no complaints.

In 2 instances the patients requested chest films because of known prolonged exposure to tuberculosis. They had no other complaints.

tuberculosis is apparent from these figures. Stiehm (7) reported an experience in a sorority house at the University of Wisconsin in which one senior student was found to have open tuberculosis. On tuberculin testing of 11 of 15 students living in the same house who had originally reacted negatively, all showed positive reactions after the known exposure. One student who had lived in the house only two weeks prior to discovery of the open case was Mantoux negative. The incidence of positive Mantoux tests in the exposed group was 93.3 per cent as compared with 25 per cent in the entire student body. Such incidents as these, together with the data in table 3, demonstrate that every precaution for prevention of transference of the tubercle bacilli from patient to nurse must be taken.

A striking feature of our study is the high incidence of a family history of tuberculosis in those nurses who later developed active disease (34.6 per cent among the group coming down with active tuberculosis as compared with 4.7 per cent among 500 healthy nurses chosen at random from equal groups of students, affiliates, postgraduates and graduates); 23.1 per cent of these active cases were in nurses who had been on duty in wards of the tuberculosis hospital. It would seem that a history of prolonged exposure to tuberculosis as thus given by 57.7 per cent of the nurses who developed active disease while on duty should receive careful attention in making decisions as to the acceptability of applicants for hospital positions.

Table 4 shows the variability and often the vagueness of the symptoms which led the nurses who had active infections to report for examination. When it is seen that nearly half of the patients reported because of loss of weight, the value of monthly weight records on all nurses seems obvious. The nine instances in which there were no complaints but the infection was discovered only by chest films would seem to justify the considerable outlay required for X-ray films on all students and all positive Mantoux reactors in the other groups, which are now being made.

CONCLUSIONS

The seven-year study revealed that the incidence of tuberculosis among nurses of the Cook County Hospital was about the same as in other similar age groups with similar exposures. Since it was found that nurses were entering the Cook County Hospital with active tuberculosis, even though each one presented a certificate of a recent satisfactory physical examination, it becomes obvious that a chest film on entrance is a necessity for all nurses regardless of their classification. It was shown that important exposure to this highly contagious disease is almost inevitable during a three-year training period and is very likely during a postgraduate or affiliating course of several months at the hospital. The Mantoux tests indicate that, in nearly 100 per cent of those previously not infected, this exposure results in enough invasion of the body to produce an allergic response. Most of these primary invasions do not result in clinically active tuberculosis but some undoubtedly do. It is clear that the hazard of developing active tuberculosis is greatest in those nurses who have had prolonged and intimate contact with tuberculosis in their homes or in caring for tuberculous patients before coming to Cook County Hospital.

The symptoms most frequently leading to the suspicion of active

tuberculosis were the usual ones of continued cough, loss of weight, undue fatigue, thoracic pain, etc., but in seven instances active tuberculosis was discovered on routine chest films when there had been no subjective or objective symptoms to arouse suspicion. The value of Mantoux tests, routine chest films and routine weight records is clearly established in discovering early cases.

NEW PROGRAM FOR TUBERCULOSIS CONTROL AMONG THE NURSES

After considering the data discussed above, the following program for prevention of tuberculosis among nurses at the Cook County Hospital, similar to that originally suggested by Myers, has gone into effect.

1. Mantoux tests are being performed on the entire nursing personnel, except upon those known already to have positive reactions (PPD). Second strength tests are performed on those reacting negatively to the first strength. For those reacting positively to the Mantoux tests an X-ray film of the chest is made, unless a chest film has already been made within six months.

2. Persons reacting negatively to the Mantoux test are retested every six months. When there is a shift from negative to positive, a chest film is made at once and a careful physical examination. If no clinical signs of tuberculosis activity are discovered, the nurse is required to report to the infirmary once a month for the next six months for a check on weight, temperature, intercurrent respiratory infections, etc.

3. All students of the Cook County School of Nursing are to have a chest film on entrance to training and at yearly intervals thereafter, including one on leaving the school, regardless of the Mantoux test. Of course, if a shift from negative to positive in tests at the six-month interval should occur before the yearly check-up, the chest film will be made sooner. Physical examinations once a year and on leaving training will be continued.

4. From this time on all affiliates will be required to bring reports of recent chest films (taken within three months of the time they come to Cook County Hospital) or to have chest films made at Cook County Hospital at cost.

5. All graduates and postgraduates are to have a physical examination on coming to Cook County Hospital and at yearly intervals thereafter. Chest films will be required on all reacting positively to the Mantoux test.

6. In considering applicants for entrance to Cook County Hospital a history of direct contact with tuberculosis in the home or in previous

hospital experience will receive especial attention, and the applicants will not be accepted unless a tuberculosis consultant agrees that all old lesions appearing on chest films are well calcified and there are no other signs of active infection.

7. The monthly weight records on all nurses remaining here for periods of six months or longer will be continued.

8. Reliable infectious disease technique will be strictly enforced in the tuberculosis hospital. In the main hospital, as soon as open tuberculosis is discovered in the wards, an easily distinguished marker will be placed on the patient's bed or chart, and such patients will be segregated in private rooms, small wards, or if these are not available in one end of the wards. Thorough precautions against contagion will be carried on with these patients. It is hoped that eventually such patients can be transferred from the regular hospital wards to a ward set aside for isolating open tuberculosis—until such time as the facilities of the tuberculosis hospital are enlarged.

9. Constantly the contagious character of tuberculosis will be taught to all nurses and internes, and the importance of the steps outlined for its prevention will constantly be reëmphasized.

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SULFANILAMIDE IN TUBERCULOSIS[1,2]

An Explanation of Certain Findings

H. J. CORPER, MAURICE L. COHN AND CLARENCE BOWER

Both the background of the discovery of prontosil in 1935 by Domagk and the mechanism of its action in combating certain diseases still remain clouded in obscurity. The life-saving nature of this therapy has left much to be desired both experimentally and in explanation This applies also to sulfanilamide, the active fraction of the prontosil molecule which has been demonstrated to be more active and less toxic. Most of the later studies have been confined to this substance and its combinations. Originally believed specific for streptococcic infections, it has been tried in a great many other disease conditions so that the literature on this therapeutic agent has grown with almost overwhelming speed within the past few years. In their recent book, Mellon, Gross, and Cooper (1) point out that pharmacological and pathological studies of the new sulfanilamide compounds have lagged, but that weak bacteriostatic effects have been demonstrated both in culture media and in body fluids. There is general agreement that the drug acts on the animal organism whereby the natural defense forces of the body are rendered better able to cope with the infection. Potentiation by the drug of the action of antiserum has been demonstrated both in culture and in the infected animal, but more satisfying evidence is needed to clarify the mechanism of its action. Even chronic toxicity effects and metabolic studies remain to be more fully explored. Excretion of sulfanilamide is chiefly through the urine and is rapid, the major part being recoverable from urine within twelve hours after an oral dose. The wide-spread use of sulfanilamide soon proved that the drug was not harmless. With the development of methods for the determination of sulfanilamide, attempts have been made to correlate the concentration reached in the body fluids with therapeutic results or with toxic manifestations. It has not yet been established whether these effects are the result of sulf-

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] This investigation was aided by Mrs. Isabel Sewall in memory of Dr. Henry Sewall.

anilamide itself or other products formed from it in the body. However, the drug penetrates rapidly, even when administered orally. One is impressed with the fact that the field is still in its infancy and that most phases of this subject can be treated with little finality at the present time.

Sensing the temptation on the part of overenthusiastic clinical therapeutists to experiment on tuberculous patients with sulfanilamide, Dietrich in 1938 (2) suggested, on the basis of a small series of animal tests, that "no drug should be adopted or abandoned on the basis of a few observations. Because of the results in this small series of experiments, however, prontosil and related chemotherapeutic agents should not be given a trial in clinical tuberculosis until a significantly large and carefully controlled mass of experimental data clearly indicates the safety of such a trial." Though his number (8) of animals was small, it was apparent to him that relatively large doses of prontosil (single daily doses of 100 mg. per kilogram of body weight) did not eradicate the tuberculosis nor halt its spread in infected guinea pigs.

However, these results did not agree with those of Rich and Follis (3), which appeared early in 1938. They used 50 guinea pigs, averaging about 400 g. in weight, and divided them into three series. Thirty-one were treated by oral administration with crystalline sulfanilamide and 28 were kept untreated as controls. The treated animals in series 1 received 100 mg. in a single dose each day; series 2, 100 mg. in the morning and 100 mg. in the evening; and series 3, 100 mg. at 9 a. m., 100 mg. at 2 p. m., 100 mg. at 6 p. m., and 200 mg. at 11 p. m. (begun three days before infection). Later, because of the appearance of toxic symptoms in the animals of series 3, the dose was reduced to 300 mg. per day. Under the conditions of the experiments, sulfanilamide exerted a striking inhibitory effect upon the development of tuberculosis in the highly susceptible guinea pig, according to the authors. They emphasize that no conclusions should be drawn regarding any possible effect of this drug upon human tuberculosis. In two short reports, Smithburn (4) concurred with Dietrich in that he observed no beneficial effects from the daily administration of 0.2 g. to guinea pigs by intraperitoneal injection, while Greey, Campbell and Culley (5) concurred with Rich and Follis in that sulfanilamide (prontylin powder) in three daily doses of 0.1 g. per os, started three days before infection, had an inhibitory effect on the development of the lesions; when the infection had been present

seventeen to twenty-four days, treatment did not alter the macroscopical appearance of the lesions. The development of sensitivity to tuberculin was unaltered by sulfanilamide therapy.

In a report by Kolmer, Raiziss and Rule (6) in December, 1938, in which they tried sulfanilamide by intramuscular administration, they could note no beneficial effect in the treatment of experimental tuberculosis in guinea pigs when begun two hours after infection. Six derivatives of sulfanilamide in the forms of their sodium salts, by muscular injection, were also without demonstrable curative effects when treatment was started nine days after infection.

Although our work on sulfanilamide and tuberculosis was in contemplation with the appearance of the early reports of successful use in other diseases and our earlier preliminary findings revealed, as did those of Dietrich and Smithburn, that the parenteral use of sulfanilamide had no appreciable effect upon experimental tuberculosis in the guinea pig, we could not reconcile this with the apparent positive findings of Rich and Follis, and Greey and colleagues except for the fact that the mode of administration played an important part in the results which then required further explanation as well as elaboration. At the outset, we were not satisfied that the dosage was the only significant feature and thus sought other evidence in addition for the differences in action.

CURVE OF SULFANILAMIDE IN THE BLOOD

We recognized early that the toxicity of sulfanilamide was low since local intracutaneous toxicity tests with saturated solutions of sulfanilamide (approximately 1 per cent) in 0.9 per cent sodium chloride solution showed no appreciable skin reaction at any time after the bleb had formed from the injection. Likewise, subcutaneous injections of 5 cc. of a saturated solution of sulfanilamide in 0.9 per cent sodium chloride solution showed no appreciable reaction and were well tolerated. At incubator temperature, these solutions upon analysis contained in 5 cc. 47 and 46 mg. of sulfanilamide (U.S.P. tested, Malinckrodt). Since we could not find satisfactory data in the literature regarding the blood concentration of the sulfanilamide following oral and parenteral administration in guinea pigs, this was studied using the Kamlet modification (7) of the Marshall, Emerson and Cutting method for the analysis of sulfanilamide content in the blood at various intervals after administration. The results of these findings for subcutaneous and oral administration are recorded in chart 1 and show that, although the injection of 50 mg. of

sulfanilamide subcutaneously results in an immediate high content in the blood (about 4.0 mg. per 100 cc. of blood) within the first half hour, there is a rapid drop so that at two hours only 2.5 mg. are present with an almost complete clearing (0.19 mg.) eight hours after injection; while after feeding 150 to 300 mg., although the amount (3.62 and 3.91 mg.) in the blood reaches about the same level within one hour after feeding (as after injection), the high level in the blood is maintained fairly well over the eight-hour period (2.22 and 1.49 mg. per 100 cc. of blood). These amounts were chosen for test since they approached the maximum

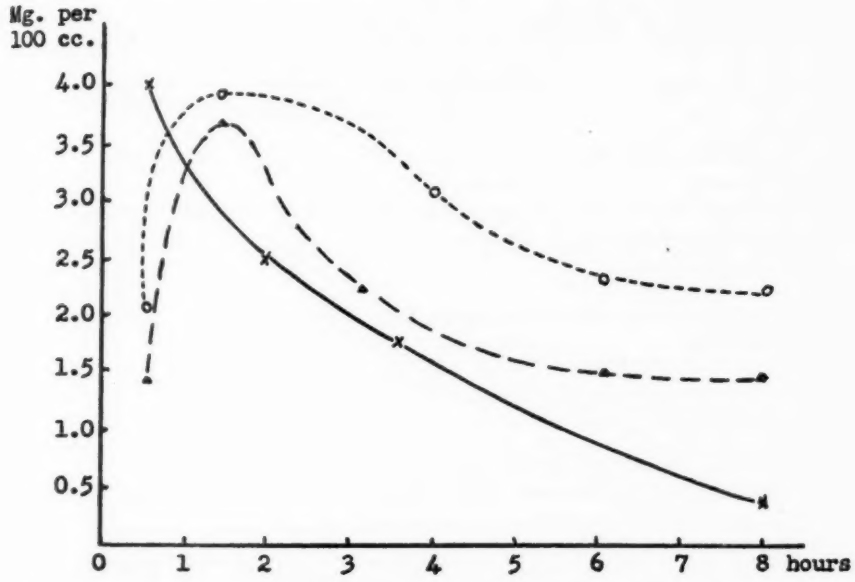

CHART 1. Time absorption of sulfanilamide into the blood-stream of guinea pig. —— 50 mg. subcutaneously – – – – 150 mg. orally ------ 300 mg. orally.

amount that could be administered by the route noted and tolerated by the normal guinea pig without significant toxic effect.

EFFECT OF SULFANILAMIDE ENTERALLY AND PARENTERALLY ON TUBERCULOSIS

In verification of the findings of Rich and Follis, and Greey, Campbell and Culley, we found, as shown in table 1, that the feeding of 150 mg. of sulfanilamide twice daily had an effect which might lead one to believe that the tuberculosis had been retarded and especially so in the spleen,

the special organ of susceptibility (8) in this animal. However, the parenteral administration in amounts consistent with experimental procedure showed very little effect, as pointed out by Dietrich, Smithburn, Kolmer, Raiziss and Rule.

Careful examination of the animals treated orally with sulfanilamide, however, did not prove as convincing that the tuberculosis had been retarded since the number of organic tubercles appeared to be just as numerous as in the controls (see figure 1) even though the spleens of the treated animals were considerably smaller. There was also noted a

TABLE 1

The effect of sulfanilamide on experimental tuberculosis† in the guinea pig

TREATMENT	TIME TREATMENT WAS STARTED WITH REGARD TO INFECTION	TOTAL AMOUNT SULFANILAMIDE GIVEN	POSTMORTEM OBSERVATIONS (AVERAGE) AND REMARKS
5 cc. saturated solution daily subcutaneously	30 days before infection	3.95 g.	3*+
150 mg. twice‡ daily 7 hours apart orally (gelatine capsules)	3 days before infection	15.9 g.	2+ to 3+. Spleens darker in color and almost normal in size. Slightly more tubercles in lungs
5 cc. saturated solution daily subcutaneously	Coincidental with infection	2.4 g.	3+
5 cc. saturated solution daily subcutaneously	7 days after infection	2.15 g.	3+
Control no treatment			3+

* Average of 6 guinea pigs in each series.

† 0.000,1 mg. subcutaneously of virulent human strain H160. All guinea pigs weighed from 300 to 500 g.

‡ This dose proved slightly toxic.

3+ tuberculosis indicates marked involvement of all organs. The guinea pigs were killed two months after infection.

peculiar deep purple-blue color of the organs and especially of the spleen that made us feel that the findings might be the result of a specific toxic effect of the sulfanilamide on the organs rather than an effect on the tuberculosis.

Effect of sulfanilamide on acute experimental tuberculosis: Since sulfanilamide exerted beneficial effects on certain acute diseases, it was thought that possibly its effects in acute tuberculosis might also show striking results as compared with the effect on the less rapidly progressive forms. Since guinea pigs given intravenous injections of highly virulent

human tubercle bacilli in large amounts (1.0 or 0.01 mg.) of fine suspension succumb early, these experiments could be carried over short periods of time only; and yet, if the sulfanilamide would have a retarding effect upon the development of the viable bacilli (9) in the animal body, both the survival time and pathological involvement or its nature should show this to some extent.

One set of 12 guinea pigs was infected intravenously, using 1.0 mg. of a highly virulent strain of human tubercle bacilli (H160, capable of infecting intravenously in one-billionth mg. amount); 4 of these animals were given subcutaneous injections of 5 cc. of a saturated solution of sulfanilamide twice daily (morning and late afternoon) begun coincident with infection, treatment being continued until the animals died (the total amount of sulfanilamide ranging from 0.8 to 1.3 g.). The guinea pigs survived as follows: 1 for eight days, 2 for nine days and 1 for thirteen days. The second group of 4 pigs of this set received 150 mg. orally in gelatine capsules twice daily (totalling about 1.8 to 2.7 g.) and survived as follows: 1 for six days, 2 for seven days and 1 for nine days. The remaining 4 (untreated controls) all survived for twelve days.

In a second set of 12 guinea pigs, the infecting amount of bacilli was reduced to 0.01 mg. of a highly virulent strain of human tubercle bacilli (H160) given intravenously. Four of these were treated subcutaneously with 10 cc. of saturated sulfanilamide solution twice daily, begun three days before infection and continued to the day of death. The total amount of sulfanilamide given was from 3 to 5 g., and the survival time was as follows: 1 for twelve days, 1 for thirteen days, 1 for nineteen days and 1 for twenty-two days. Beginning three days before infection, the second group of 4 guinea pigs of this set received orally 150 mg. of sulfanilamide in capsules twice daily, totalling 4.2 g. All of the guinea pigs in this group died on the eleventh day after infection, while the remaining 4 guinea pigs as untreated controls survived for eight, twelve, sixteen and seventeen days respectively.

In the first set, infected with the large (1.0 mg.) amount of tubercle bacilli, all the treated and untreated animals showed very little discrete gross lesions besides an acute tuberculous pneumonia; while in the second set infected with the smaller (0.01 mg.) amount and surviving longer, most of the organs began to reveal innumerable small discrete tubercles, particularly in the lungs. However, there was no perceptible difference between the treated and the untreated animals or those treated enterally

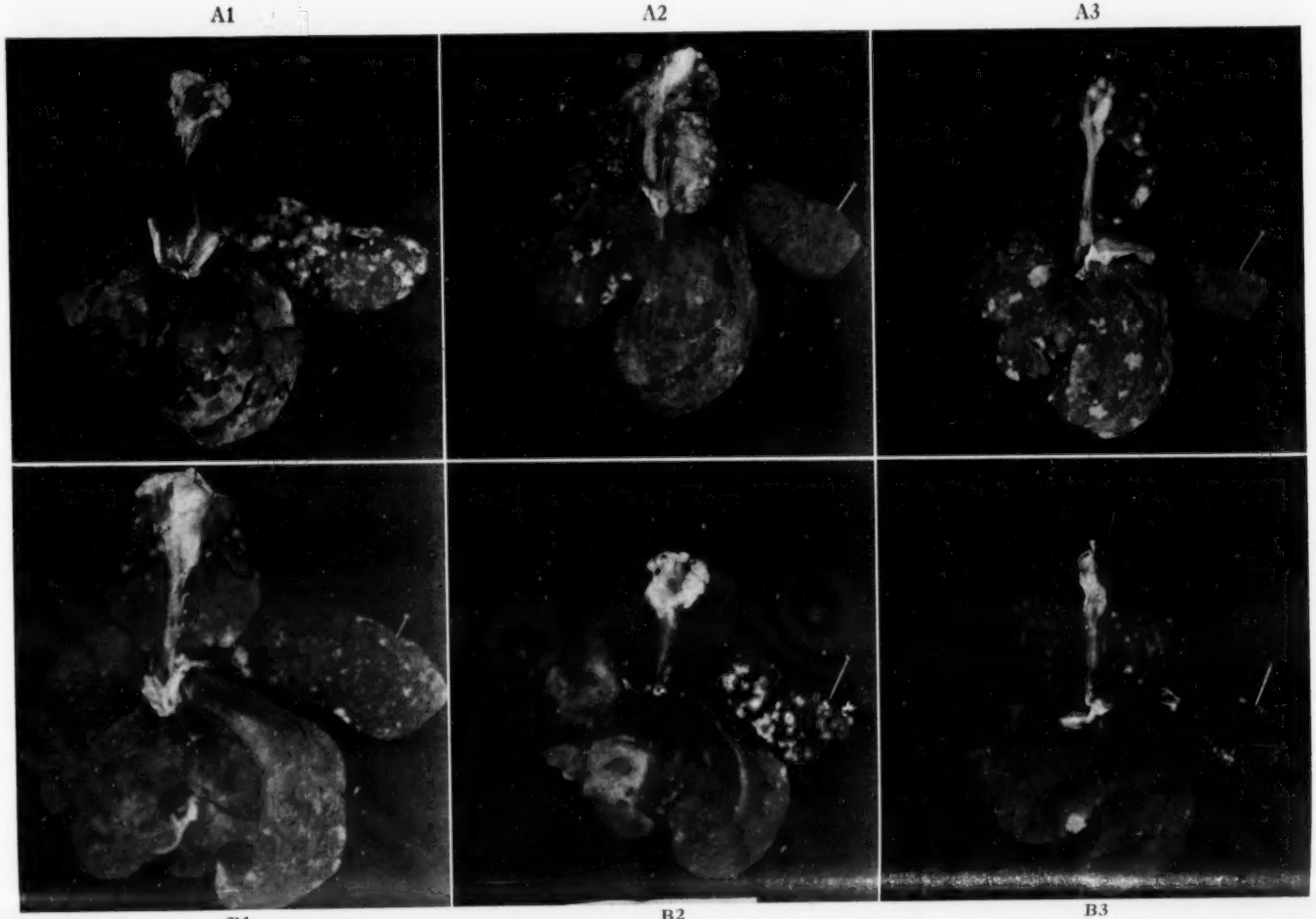

FIG. 1

or parenterally. It was noted, however, that the duration of life of the sulfanilamide treated animals was slightly shorter than that of the infected untreated controls.

Effect of sulfanilamide on chronic tuberculosis: In a third set, a relatively smaller intravenous infecting dose (0.000,01 mg.) of virulent human tubercle bacilli (H160) was used so that the guinea pigs would survive sufficiently long to determine the effect of the sulfanilamide enterally on the milder, less progressive type of infection as compared with the parenteral (subcutaneous injection) administration. Four of 12 animals were treated twice daily by giving subcutaneously 5 cc. of a saturated solution of sulfanilamide, beginning three days before infection and continuing daily throughout the experimental period. One of these guinea pigs died on the twenty-ninth day as a result of extraneous factors and the remaining 3 were killed two months after infection, each having received a total of 6.3 g. of sulfanilamide. They showed a marked tuberculous involvement of the spleen, liver and lungs (the spleens of the 3 guinea pigs respectively measured 4.5 x 2.0 cm., 4.5 x 2.5 cm., and 3.8 x 1.8 cm.). The second 4 guinea pigs were treated twice daily by giving 150 mg. of sulfanilamide in gelatine capsules orally at each treatment, begun three days before infection and continued throughout the entire period of two months after infection so that a total of 18.9 g. of sulfanilamide were received by each animal. In general, however, they revealed about the same amount of tuberculosis at postmortem as the foregoing parenterally treated animals, with this exception, that the spleens were found to be smaller, respectively measuring 3.0 x 1.0 cm., 3.0 x 1.3 cm., 3.0 x 1.5 cm. and 3.0 x 1.5 cm., the tubercles appearing definitely smaller in these spleens than in the parenteral animals. The third group of 4

FIG. 1. The effect of sulfanilamide on organic tuberculosis in the guinea pig. Top row: A1, infection control: result two months after the intravenous injection of 0.000,01 mg. of virulent human tubercle bacilli (H160). A2, same infection as A1 treated by subcutaneous injection twice daily of 50 mg. (5 cc. saturated solution) sulfanilamide begun three days prior to infection. A3, same infection as A1 treated with 150 mg. sulfanilamide by mouth twice daily begun three days prior to infection. Note the striking difference in the size of the spleen but the tuberculosis is not retarded as a whole.

Lower row: B1, infection control: result two months after the subcutaneous injection of 0.000,1 mg. of virulent human tubercle bacilli (H160). B2, same infection as B1 treated by subcutaneous injection once daily of 50 mg. of sulfanilamide begun one month prior to infection. B3, same infection as B1 treated with 150 mg. sulfanilamide by mouth twice daily begun three days prior to infection. Note the reduced size of the spleens of the sulfanilamide treated animals and especially of the orally treated B3 as compared with the control, but the extent of the organic tuberculosis as a whole has not been retarded.

guinea pigs was not treated and served as infection controls, showing two months after infection what might appear to be more tuberculous involvement than the sulfanilamide treated guinea pigs. The spleens measured 4.5 x 2.0 cm., 4.5 x 2.5 cm., 5 x 2.5 cm. and 5.5 x 3.5 cm. respectively, and were completely studded with tubercles.

In vitro effect of sulfanilamide upon human tubercle bacilli: In direct cidal-static tests (10) for the effect of prontosil and sulfanilamide on the survival of human tubercle bacilli, it was found that, after exposure to a saturated solution of sulfanilamide (about 1 per cent) for one to twenty-four hours at 37°C. (of an equal volume of a suspension containing 0.000,01 mg. per cc.), there was no effect upon the viability of the bacilli; likewise, a 2.5 per cent solution of prontosil in saline was without effect. It would appear from this that whatever effect was observed, it could hardly be attributed to a direct effect of these drugs upon the tubercle bacilli.

In view of the fact that a remote anticatalase effect of sulfanilamide was suggested by Locke, Main and Mellon (11), we tried the effect of hydrogen peroxide in the same type of test as used above and found that exposure of a fine suspension of human tubercle bacilli (0.01 mg. per cc.) for thirty minutes at 37°C. to an equal volume of 1 per cent hydrogen peroxide for thirty minutes at 37°C. was without effect upon the viability of these bacilli. The significance of this action thus far can be of theoretical interest only.

The organic effect of sulfanilamide in tuberculosis: Since sulfanilamide when given parenterally had no marked effect upon tuberculosis and since its effect enterally upon tuberculosis might be more apparent than real, it seemed highly desirable that more information be sought regarding the enteral consequence which would rule out as far as possible an effect upon tuberculosis (12), from the standpoint of the tubercle bacilli at least. Since dead and avirulent tubercle bacilli can be relied upon to produce certain results in the animal economy, which rule out the possible effect on tuberculosis *per se* as produced only by virulent (multiplying) tubercle bacilli, an experiment was planned in which the effect of large doses of sulfanilamide *per os* were studied upon the spleen in normal guinea pigs, in guinea pigs given intravenous injections of large amounts (50 mg.) of heat-killed avirulent human tubercle bacilli or intravenous injections of large amounts (25 mg.) of viable avirulent human tubercle bacilli (9). These amounts of heat-killed or avirulent tubercle bacilli given intravenously produce no tuberculosis in the guinea pigs but cause

a transient marked splenomegaly which shows a gradual subsidence within six to nine months after injection.

In general, there was observed a marked dark bluish appearance of many of the internal organs, particularly the spleen, of the animal

TABLE 2

The effect of sulfanilamide upon the spleen size in acute splenomegaly in the guinea pig

PRIMARY INJECTION	TREATMENT-SULFANILAMIDE	SPLEEN WEIGHT	AVERAGE WEIGHT IN GRAMS AND APPEARANCE OF SPLEEN
		grams	
None		0.8	0.85
		0.8	
		1.1	
		0.7	
None	150 mg. twice daily, early morning and late afternoon	1.0	0.88, dark red in appearance
		0.7	
		0.9	
		0.9	
50 mg. avirulent human tubercle bacilli heat-killed boiling water bath 30 minutes		1.0	1.90, enlarged but normal color
		2.0	
		2.6	
	150 mg. twice daily, early morning and late afternoon	1.0	1.0, dark red in appearance
		0.7	
		1.6	
		0.7	
25 mg. avirulent human tubercle bacilli		3.0	2.8, enlarged but normal color
		4.3	
		1.5	
		2.5	
	150 mg. twice daily, early morning and late afternoon	1.6	1.7, slightly enlarged, dark red
		1.8	
		1.8	

All guinea pigs were treated one week before injection of bacilli and received a total of 7.5 g. of sulfanilamide. They were killed twenty-five days after the injection of the bacilli.

whether normal or those given the intravenous injections of the heat-killed or viable avirulent human bacilli that had been given the sulfanilamide *per os* as compared with those not given this treatment. Since the spleen was most strikingly affected and since this organ in the guinea pig plays a conspicuous part in tuberculosis (8), the weight of the spleen

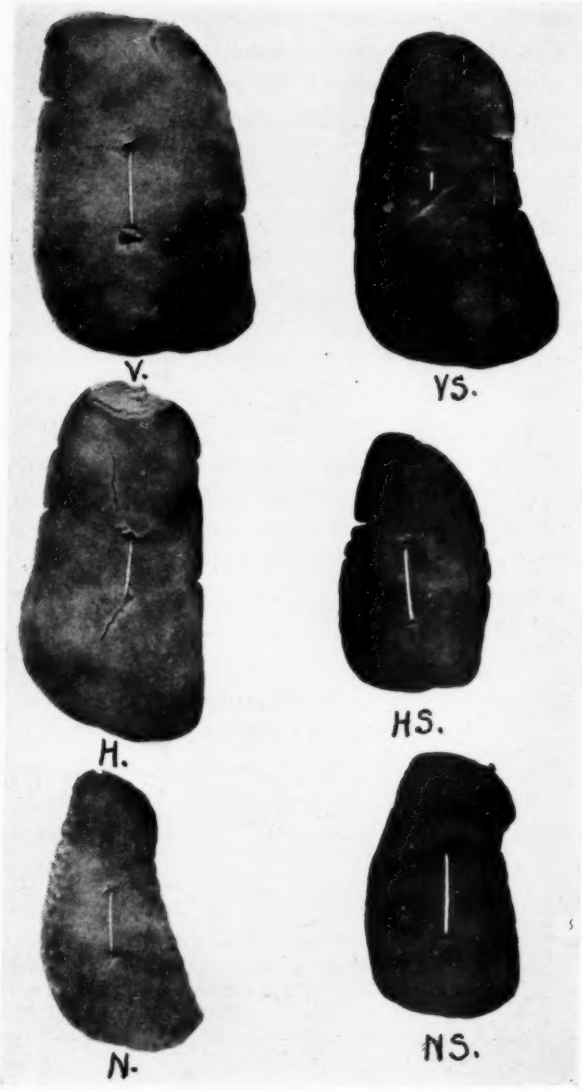

FIG. 2. The effect of sulfanilamide *per os* upon the size of the spleen in normal guinea pigs and those given intravenous injections of heat-killed and viable avirulent human tubercle bacilli. N and N.S. are respectively the normal spleen and the spleen from an animal given 150 mg. of sulfanilamide twice daily for twenty-five days. H and H.S. are respectively the spleen from guinea pigs given an intravenous injection of 50 mg. of heat-killed tubercle bacilli and H.S. treated with sulfanilamide as was N.S. V and V.S. are respectively the spleen from guinea pigs given 25 mg. of viable avirulent tubercle bacilli and V.S. treated with sulfanilamide as was N.S. Note the darker hue of the sulfanilamide spleens and the diminished size of those that received tubercle bacilli and were treated with sulfanilamide (see table 2).

was determined and is recorded in the table. While the spleen in the normal guinea pig shows no appreciable change in weight from that in

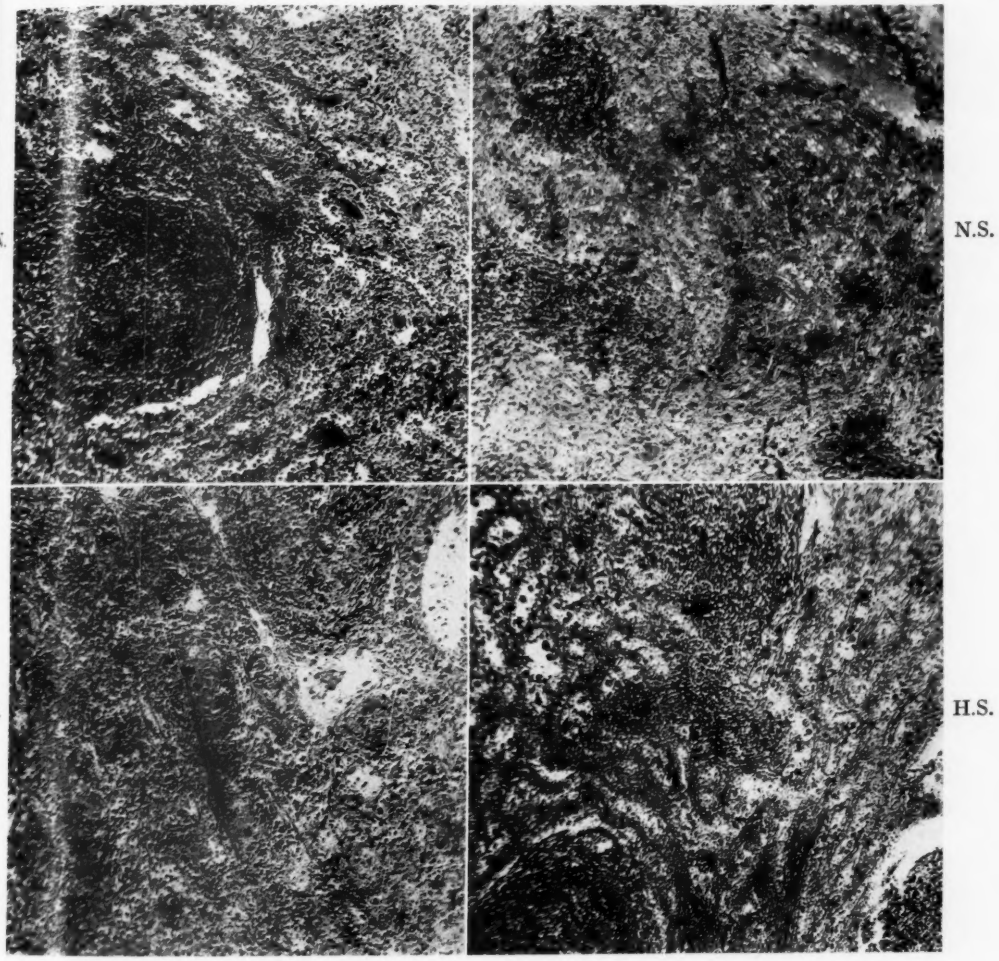

FIG. 3. Photomicrographs (low power) of spleens N and N.S. and H and H.S. of fig. 2. Note the congestive and aplastic effect in N.S. as compared to N and the suppression of the natural monocytic hyperplastic reaction to the tubercle bacilli in H.S. as compared with H. The sulfanilamide treatment appears to retard the natural tubercle reaction by a toxic effect upon the specific cells in the spleen. It does not appear to have any effect on infection by viable virulent tubercle bacilli.

the animal given sulfanilamide, those obtained from guinea pigs receiving intravenous injections of heat-killed or viable avirulent tubercle bacilli

were decidedly heavier in the animals which had not been treated with sulfanilamide enterally as compared with the spleens of the guinea pigs which had been treated.

HISTOLOGICAL CHANGES IN THE SPLEEN

The histological study of the spleens of the guinea pigs recorded in table 2 bore out the impressions that the effect seen in the tuberculous animals was due to the toxic action of the continued administration of the sulfanilamide over long periods. In a recent article, Shecket and Price (13) found a toxic granulocytopenia with arrest of the maturation of the blast-forms of the myeloid series resulting from the toxic action of sulfanilamide in man. The liver and spleen were dark red and congested and revealed a haemosiderosis. They believe this anaemia in man to be of a haemolytic nature rather than an idiosyncrasy and that long duration administration of the drug is a factor. Briefly, the spleens from the sulfanilamide animals as compared with the normal guinea pigs showed a striking leucotoxic action, which was evident in the reduction of nucleated elements; and, while the usual effect of the large deposits of both heat-killed and viable avirulent tubercle bacilli were evident in a marked proliferation of the large monocytic cells, the sulfanilamide treatment (although not as strikingly toxic to these cells as to the granulocytes) showed a decided effect, as evidenced by the greater comparative paucity even of these cells. These findings also make it highly probable that the effect seen is not on the tuberculosis, but it is organic and is on the tubercle forming cells. (See illustrations.)

SUMMARY AND CONCLUSIONS

1. Large administrations of sulfanilamide over long periods of time, parenterally as well as enterally, begun before or coincident with infection of guinea pigs with virulent human tubercle bacilli have an apparent, though not real, effect upon the organic tuberculous involvement of these animals which is most strikingly evident in the spleen. These findings explain the earlier, cautiously presented studies on enteral treatment by Rich and Follis, and subsequently by Greey and colleagues, which could not be verified by parenteral sulfanilamide treatment studies.

2. The apparent effect noted upon the tuberculosis in the guinea pig is explained as an organic toxic effect of the sulfanilamide since it can also be noted when heat-killed and avirulent human tubercle bacilli

are given intravenously in large amounts to animals which are treated as compared with untreated controls.[3]

3. Even in large doses, sulfanilamide has no appreciable effect upon the spread of tuberculosis in guinea pigs infected by various routes and in various ways with virulent human tubercle bacilli; such effect as is seen can be entirely explained on the basis of the toxic effect of the sulfanilamide and not upon a retardation of the tuberculosis.

4. In elaboration of the view expressed by Shecket and Price (1939) that "the use of sulfanilamide in conditions in which its value is not established should be reserved for cases under institutional direction" and that the drug should not be used for long duration administration, we should like to add that misinterpretation of the effect in chronic diseases especially be avoided by carefully controlled experimental studies considering the organic toxic action of the drug before application to human treatment.

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CASE REPORTS

SILICO-TUBERCULOSIS IN STEVEDORES[1]

Report of Two Cases

HAROLD L. ISRAEL AND H. W. HETHERINGTON

Silicosis is not commonly considered an occupational hazard of stevedores. Recently we encountered two dock workers with pulmonary tuberculosis whose clinical course and X-ray examination suggested an underlying pneumonoconiosis. At first serious consideration was not given to the possibility of silicosis, since neither patient gave a history of work in the occupations in which silicosis is frequent. Later, inquiry revealed that both men had worked for many years unloading cargoes of clay imported for the manufacture of pottery. The clay, which was of the consistency of flour, was shovelled into large buckets, in an extremely dusty atmosphere.

Case 1: J. S., a white German male, aged 38 years, who had worked as a stevedore for the past fifteen years, visited the Dispensaries of the Henry Phipps Institute on April 22, 1937 complaining of cough, weakness and dyspnoea on exertion since an attack of "influenza" three months before. There had been pain in the left upper chest for three months and weight loss of 20 lbs. The patient was thin, but not manifestly ill. Temperature, pulse rate and respiratory rate were normal. Physical findings included impaired resonance, distant bronchovesicular breath sounds and posttussive râles over the upper half of the chest on both sides. There were bilateral cervical scars resulting from incision and draining of enlarged lymph nodes in childhood. The tuberculin test was positive, two-plus to 0.000,02 mg. PPD. The sedimentation rate was 30 mm. in one hour. The Kahn test was negative. Sputum examination on three occasions revealed tubercle bacilli (Gaffky I, II and V).

X-ray examination (figure 1) showed dense confluent spots and strands with areas of rarefaction suggesting emphysema in the upper two-thirds of both lungs. At the right apex there was a cavity measuring 2 by 3 cm. In the lower third of both lungs there were irregularly distributed, grouped

[1] From the Henry Phipps Institute, University of Pennsylvania and the Department of Tuberculosis, Philadelphia General Hospital, Philadelphia, Pennsylvania.

and scattered spots, most numerous near the heart. Both lung bases showed increased radiotranslucency due to emphysema. The diaphragm was horizontal, irregularly peaked and adherent to the lateral chest wall on both sides.

The extent and symmetrical distribution of the lesion, with distortion of the diaphragm and well marked emphysema, suggested silico-tuberculosis, but in the absence of history of dust exposure, a diagnosis of far advanced pulmonary tuberculosis with probable haematogenous dissemination was made. The patient spent eight months on the service of Dr. C. A. Heiken in the Department of Tuberculosis of the Philadelphia General Hospital, leaving without consent. While in the hospital he developed a perirectal abscess. Clinical and X-ray examination on April 18, 1938 showed no change from the examination made a year earlier. The chronic course of the disease without deterioration of health was not typical of advanced tuberculosis. The prominence of dyspnoea, as well as the appearance of the lesion on X-ray examination, suggested pneumonoconiosis, and further inquiry revealed the history of exposure to silica-containing dusts.

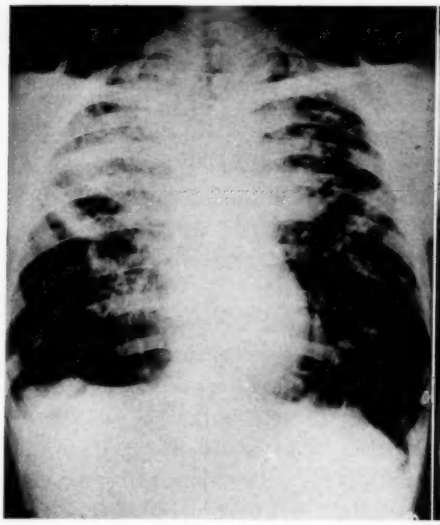

FIG. 1. Case 1. April 22, 1937

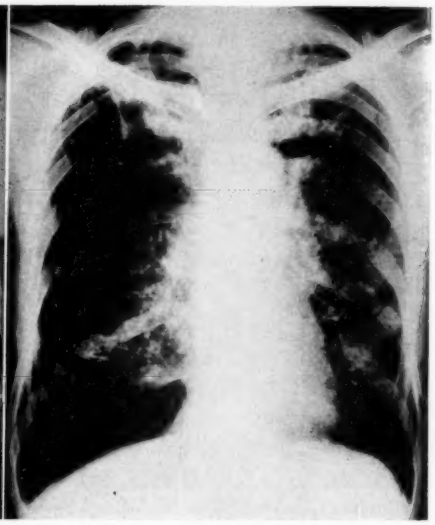

FIG. 2. Case 2. August 9, 1938

Further observation for one year has shown no change in the patient's condition, and a diagnosis of silico-tuberculosis has been made.

Case 2: P. J., a white American male, aged 53 years, who had worked as a stevedore for the past thirty-seven years, was admitted to our service in the Department of Tuberculosis of the Philadelphia General Hospital on June 27, 1938. Chief complaints were cough and scant expectoration of six months'

duration and a weight loss of 20 lbs. The patient appeared thin, weak and toxic. The temperature was 100° F., the pulse rate was 100 and the respiratory rate was 40. Physical findings included impaired resonance and bronchovesicular breath sounds over the entire right chest and the upper third of the left chest. Râles were audible at the right apex. The Kahn test was negative. Sputum examination revealed tubercle bacilli (Gaffky IV). The patient left the hospital without consent shortly after admission, before X-ray examination could be made. He returned to the hospital on August 8, 1938, complaining of severe dyspnoea of two weeks' duration and pain in the right chest of four days' duration. X-ray examination (figure 2) showed a small pneumothorax space over the lower four-fifths of the right lung. The lung was densely adherent to the chest wall above the clavicle. Close-set sharply defined spots were present throughout the partially collapsed lung, with a cavity measuring 2 x 1 cm. at the level of the clavicle. Similar spots were present throughout the left lung. There was moderate bilateral emphysema.

Pneumonoconiosis was suspected, and further questioning of the patient disclosed that during much of his thirty-seven years as a stevedore he had worked on cargoes of clay imported for use in making china ware.

The patient left the hospital on September 14, 1938 and died at home on October 30, 1938. Although confirmation by necropsy was not obtained, a diagnosis of silico-tuberculosis seems justified.

SUMMARY

Two instances are reported in which stevedores developed lesions typical of silico-tuberculosis. Both men gave histories of prolonged exposure to dust while at work unloading clay imported for the manufacture of pottery.

SULFANILAMIDE IN CLINICAL TUBERCULOSIS[1]

H. R. NAYER AND M. MAXIM STEINBACH

After careful trial of sulfanilamide in experimental tuberculosis in the guinea pig, Steinbach and Dillon (1) concluded that the drug was of no value. This is in agreement with Dietrich (2), Smithburn (3), and Kolmer (4). Some months ago, however, Rich and Follis (5) reported very favorable experimental results. This report encouraged us to test the drug in clinical tuberculosis in man. We selected 8 adult males with advanced lesions. Other methods of treatment had failed in these cases. (See table 1.)

The drug was administered for approximately two months, except that in one patient it had to be discontinued after ten days because of toxic symptoms. Since we had no experience as to dosage of sulfanilamide in this disease, large amounts were given during the first week, and during the following three weeks smaller doses were administered. The dosage was raised for a few days at the beginning of the second month, and gradually decreasing amounts were given during the remainder of the period. Table 2 shows the number of days of treatment and the total amount of drug given. During the first three or four days, the total daily dose was divided into six equal portions and administered every four hours. Thereafter the daily dose was divided into four parts and given during the day. Equal doses of sodium bicarbonate were given to combat the tendency towards acidosis which has been observed with sulfanilamide. Clinical observations were made daily; X-ray films of the chest were taken frequently; and laboratory studies showed the following: In one case the haemoglobin dropped from 84 per cent to 60 per cent. There was no other instance of significant change in the blood. The carbon dioxide combining power of the blood remained normal during treatment. Urine remained unchanged.

Mild cyanosis was observed in every case. This was most intense during the first few days and persisted throughout to some degree. It disappeared completely within twenty-four to forty-eight hours after the drug was stopped. Headache, nausea and anorexia were noted in varying degree in several of the patients. A rise in temperature to 101° F. occurred in one patient (case 8). With the exception of case 7, already mentioned, the toxic symptoms were mild and did not warrant discontinuing the medication.

All patients remained under observation from one to five months after

[1] From the Division of Pulmonary Diseases, Montefiore Hospital, New York City.

the sulfanilamide was stopped. There was no significant effect on the pulmonary disease—neither progression nor retrogression. Cough, sputum and

TABLE 1

CASE NUMBER	AGE	TYPE OF DISEASE (X-RAY)	DURATION OF DISEASE
	years		
1 (W. B.)	21	Extensive bilateral fibrocaseous upper lobe tuberculosis with scattered nodular infiltrations throughout both lower lobes	1 year
2 (A. B.)	25	Bilateral fibrocaseous tuberculosis with cavities of both upper lobes	6 years
3 (J. L.)	26	Extensive bilateral fibrocaseous tuberculosis with upper lobe cavities	6 months
4 (A. R.)	35	Bilateral fibrocaseous tuberculosis with cavities in both upper lobes	7 years
5 (I. B.)	59	Extensive nodular infiltrations in all lobes; bilateral orchidectomy for tuberculosis eighteen years ago	24 years
6 (H. P.)	24	Extensive disseminated bilateral nodular tuberculosis	4 years
7 (I. W.)	51	Bilateral fibrocaseous tuberculosis with cavities of upper lobes	4 years
8 (M. S.)	23	Bilateral fibrocaseous tuberculosis with cavities of upper lobes	8 months

TABLE 2

CASE	TOTAL AMOUNT OF SULFANILAMIDE GIVEN	DAYS OF ADMINISTRATION
	grams	
1	179	71
2	88.6	46
3	127.7	64
4	142.7	61
5	133.7	62
6	185.3	61
7	26	10
8	140	58

First two days the total daily dose was 5 grams; next six days, 4 grams; next four days, 3 grams; the next sixteen days, 2 grams; next five days, 4 grams; next seven days, 3 grams; and for thirty-one days, 2 grams.

laboratory signs of activity remained essentially unchanged. There was a slight tendency to weight loss in some of the cases, probably due to the anorexia. Serial roentgenograms of the chest, taken before, during and after administra-

tion of the sulfanilamide, showed no significant changes, except in two instances where there was possible slight progression. This latter condition may be expected in this type of case, with or without treatment.

SUMMARY AND CONCLUSIONS

1. Eight patients with extensive bilateral pulmonary tuberculosis were treated with sulfanilamide for a period of from ten to seventy-one days.

2. As far as we could evaluate the results, there was no apparent effect, either beneficial or harmful, upon the disease.

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TUBERCULOUS ABSCESS OF THE CERVICAL SPINE[1]

A Case with a Communication between the Abscess and an Oesophageal Diverticulum

MORRIS A. BRAND

This is a presentation of the clinical and pathological findings in a patient with a Pott's abscess communicating with a diverticulum of the oesophagus.

J. S., male, was admitted to the Montefiore Hospital on February 29, 1936, complaining of pain in the left chest and left arm, recent onset of fever, weight loss and weakness. The patient was apparently well until the winter of 1930 at which time he developed a productive cough with sharp inspiratory pain in the left chest. The sputum was negative for tubercle bacilli. A diagnosis of dry pleurisy was made. The cough and pain subsided and the patient returned to work. He felt well until the fall of 1932 when because of the recurrence of pain he applied to the Kings County Hospital Clinic for treatment. A roentgenogram of the spine on November 1, 1932 showed, "Compression of the bodies of the 6th and 7th cervical vertebrae with resulting kyphosis due to Pott's disease. There is also a fibro-nodose tuberculous lesion in both apical areas with widening of the mediastinum in this area, as associated with a paravertebral abscess." Since July, 1935 the patient noted in addition to the pain a rapid loss of weight, progressive weakness, pain in the legs, precordial pain, palpitation, pain in the left shoulder with limitation of motion at that joint, fever up to 102° F. and occasional choking and sticking pain in the throat while swallowing liquid or solid food.

The patient was an elderly white male with a marked kyphos at the upper dorsal spine. There was tenderness in the second left intercostal space. Dulness was present above the first left interspace with hyperresonance throughout the remainder of the left lung anteriorly. Posteriorly in the left side there was flatness from the apex down to the seventh dorsal vertebra. Harsh tracheal breathing was heard at the left parasternal line in the second interspace. Crepitant and coarse râles were present at the left base. There were no unusual findings in the right side. There was limitation of motion of the left shoulder joint. The finger ends were clubbed and the nails curved. Haemoglobin was 54 per cent, red blood cells 3,800,000, white cells 18,750 (normal distribution), blood sugar and urea were normal, Wassermann and

[1] From the Division of Pulmonary Diseases, Montefiore Hospital, New York City.

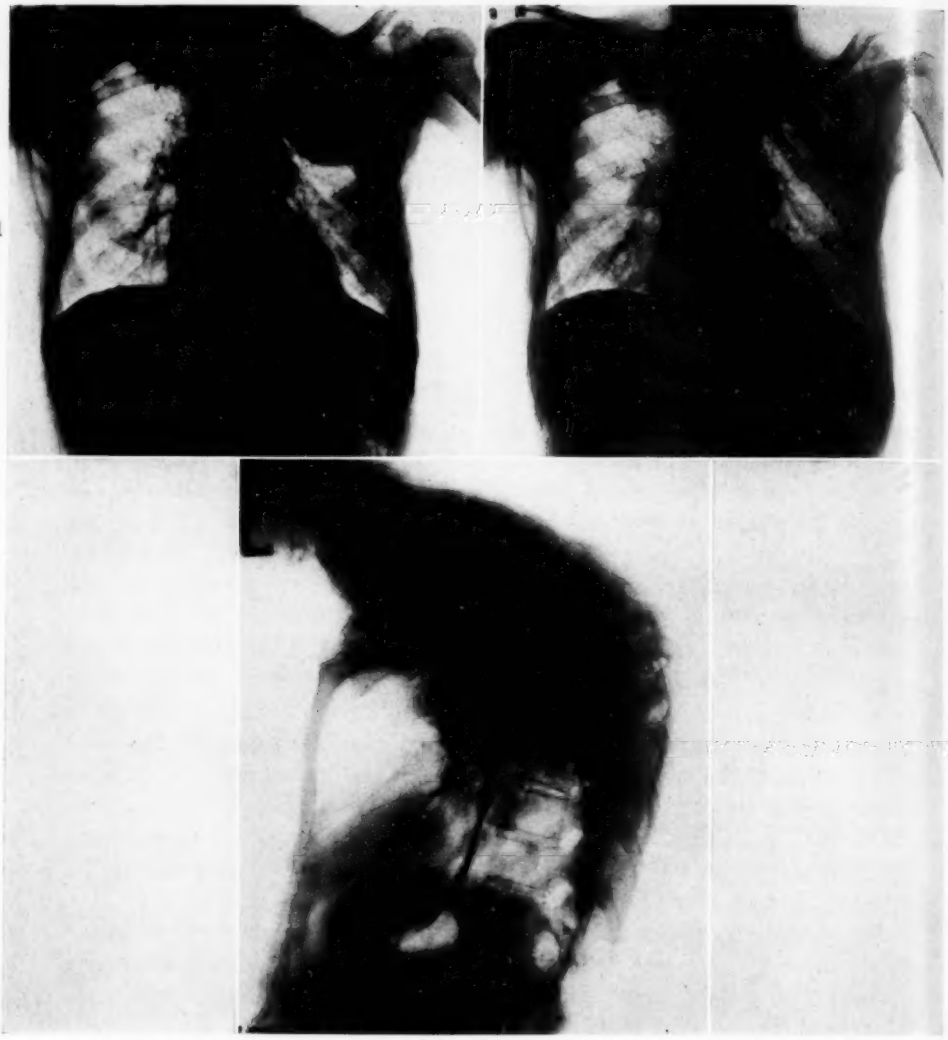

FIG. 1

FIG.

FIG.

FIG. 1. Roentgenogram of chest showing the dense circumscribed mass occupying the upper one-third of the left chest and the fibro-calcific tuberculosis involving the apex of the right lung.

FIG. 2. Roentgenogram of the oesophagus following the ingestion of contrast medium. Left lateral view: the dense mass occupying the upper posterior portion of the chest and the severe degree of kyphosis at the upper thoracic spine can be seen. The barium paste can be seen filling the diverticulum, beyond which there is a small amount of barium in the paravertebral abscess.

FIG. 3. Roentgenogram of the chest after thoracocentesis showing the encapsulated pyopneumothorax.

Kahn were negative, sedimentation reaction 29 mm. in one hour (Cutler), sputa were negative for tubercle bacilli. Urine contained two-plus albumin, an occasional granular cast and a few white blood cells.

Roentgenogram of the chest (figure 1) reveals a dense circumscribed oval mass, 6 x 9 cm., in the upper left chest, extending from the apex down to the lower border of the second rib. The lower border of this mass is sharply defined. There is no erosion of the ribs. The left hilar lymph nodes are moderately prominent in addition to which there are some dense shadows in this region. There is a single very dense nodular shadow just above the anterior end of the left first rib. In the right lung there are several diffusely scattered small irregular dense masses in the apical region. Throughout the lower half of both lungs several very small sharply circumscribed dense shadows are seen. The bronchial markings to both bases are accentuated. Roentgenogram of the spine showed a sharp kyphosis due to collapse of the bodies of the seventh cervical and the first and second thoracic vertebrae with obliteration of the bony landmarks and intervertebral spaces. Examination of the oesophagus by means of a barium meal reveals (figure 2) the contrast medium outlining the entire tube. At the level of the angulation of the spine the oesophagus is also angulated and somewhat widened. Extending upward and backward from this portion of the organ there is a triangular barium filled diverticulum, 3 cm. in length, the narrowed apex of which is turned sharply upward and appears forked. A small amount of isolated contrast medium is seen several millimetres distant from this irregular apex.

A thoracocentesis was done at the level of the fourth dorsal vertebra at the left midscapular line, and at a depth of 4 cm. a firm calcific mass was felt. Firm pressure was necessary to penetrate this. Two hundred cubic centimetres of very thick, light greenish, purulent fluid with a fecal odor was aspirated. Radiographic study (figure 3) revealed an encapsulated pyopneumothorax in the upper left chest, but whether this was intra- or extrapleural could not be determined. The fluid on smear contained large and small gram positive cocci in pairs and short chains with a moderate number of gram negative fusiform bacilli. No tubercle bacilli were present. Culture revealed *Streptococcus gamma*, diphtheroids and fusiform bacilli. There was marked diminution of pain with increased mobility at the shoulder. Subsequently several aspirations were done to relieve the patient. On May 13, 1936 the liver and spleen were found to be enlarged and a Congo red test revealed 100 per cent retention of the dye in the tissues. The patient's course was thereafter rapidly downhill and on June 6, 1936, following a severe coughing seizure associated with marked dyspnoea, he died.

Postmortem examination revealed: (*1*) tuberculosis of the sixth and seventh cervical and the first thoracic vertebrae with marked cervico-thoracic kyphosis; (*2*) left paravertebral abscess, encapsulated empyema with perforation into the left upper lobe and lung abscess; (*3*) diverticulum of the oesophagus with perforation into the empyema cavity; (*4*) healed apical tuberculosis; (*5*)

amyloid disease of the liver and spleen; (*6*) healed tuberculosis of the second and third lumbar vertebrae; (*7*) bronchopneumonia. The upper part of the left lung was displaced away from the upper part of the pleural cavity and formed a shelf at the junction of the upper and middle third of the pleural cavity, the area above this was occupied by a mass which, when opened, was found to contain a very foul smelling turbid fluid and amorphous material. There was a communication from this empyema to the oesophageal diverticulum, another to the paravertebral area adjacent to the collapsed vertebrae and a third opening into the adjacent compressed lung tissue. The surrounding pleura was markedly thickened. The remainder of the pleura was normal. On section, there were several communicating abscesses in the upper lobe and also an encapsulated caseous area one centimetre in diameter. The right lung revealed emphysema, moderate congestion, several patchy areas of bronchopneumonia and a single calcified nodule at the apex. The lower cervical and the first dorsal vertebrae were completely collapsed and appeared necrotic, and both to the right and left of these there were accumulations of purulent material which in turn communicated with the empyema cavity. The oesophagus was drawn to the left and at the point where it crossed the apex of the pleural cavity there was a small diverticulum, the tip of which communicated with the empyema cavity.

A search through the medical literature failed to reveal a case similar to the above. In 1859, MacLachlin (1) reported a case with an oesophago-pleurothoracic fistula with the abscess pointing below the patient's left breast. Osler (2), in 1898, described a case of oesophago-pleuro-thoracic fistula. In 1900, Engelkin (3) described an instance of tuberculous caries of the seventh cervical and upper dorsal vertebrae with compression of the left brachial plexus by a paravertebral abscess. A case of an oesophageal diverticulum communicating with an abscess in the right lung was reported by Provost and Leblanc (4).

In the above case it is to be assumed that two pathological processes took place independent of each other but both due to tuberculosis. The empyema was caused by the migration of the paravertebral abscess into the pleural space and the diverticulum was secondary to the traction of tuberculous paraoesophageal lymph nodes. Rupture of the tip of the diverticulum into the abscess then took place with a resultant secondary bacterial infection. The latter communication was too small to permit emptying of the abscess contents.

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SPONTANEOUS PNEUMOTHORAX[1, 2]

Aetiological Considerations

J. J. KIRSHNER

Spontaneous pneumothorax has had a long and interesting history in medical literature. The term pneumothorax was introduced by Itard in 1803. Laennec (1) in 1819 was the first to diagnose pneumothorax in the living. In his book he discusses pneumothorax exhaustively. Most of the cases of pneumothorax that Laennec saw were associated with tuberculous empyema and, like other clinicians of his day, he believed pneumothorax was the result of the decomposition of the pus and of the absorption of the fluid. This was disputed, and in 1834 Houghton laid down the dictum that where pneumothorax exists the air had been introduced from without. Laennec, however, also knew of nontuberculous pneumothorax, for in his book (1) he discusses a case of emphysema in which there was a pneumothorax due to the rupture of air cells and pleura. In his vast experience, both pathological and clinical, very little escaped him. He even discusses two cases of bilateral simultaneous pneumothorax or, as he calls it, double pneumothorax. One occurred in a man of sixty in whom the accident proved fatal within a short time and whose autopsy revealed no signs of pulmonary disease. The other case was that of a young patient with miliary tuberculosis.

The reports of investigators who followed Laennec emanated from tuberculous hospitals and the frequency of pneumothorax observed in the tuberculous patients gave pneumothorax a tuberculous significance. In 1887, Hall (2) reported the first series of spontaneous pneumothorax in the healthy. Riesman and Fussel (3) in 1902 and Emerson (4) in 1903 were the first to report nontuberculous pneumothorax in this country. However, due to the regular occurrence of spontaneous pneumothorax in tuberculous cases under observation and due to the fact that spontaneous pneumothorax occurring in the healthy was seen in private practice and did not reach the literature, it is not surprising that spontaneous pneumothorax has always had a tuberculous significance—being placed in the same category as pleural effusion. The teaching was to regard spontaneous pneumothorax as tuberculous unless proved to be otherwise. Indeed with the advent of artificial pneumothorax,

[1] From the Department of Diseases of the Chest, Jefferson Hospital and Medical College, and Medical Service No. 1, Mt. Sinai Hospital, Philadelphia, Pennsylvania.

[2] Presented at a meeting of the Laennec Society, Philadelphia, Pennsylvania, March 28, 1939.

many clinicians urged the maintenance of the spontaneous pneumothorax by artificial means so as not to allow a small tuberculous lesion to progress. Many cases were given the stigma of tuberculosis and sent to tuberculosis sanatoria when they were perfectly free from tuberculosis.

The voluminous literature on the subject in the last five years, however, has altered our impression of spontaneous pneumothorax. To-day we recognize two types of spontaneous pneumothorax—that due to pulmonary disease and the other, the idiopathic variety. The first or symptomatic type has been found to occur in all types of chest disease, the commonest of course being tuberculosis. In children, spontaneous pneumothorax is often seen in cases of streptococcic or staphylococcic bronchopneumonia with the development of a pyopneumothorax.

Recently we (5) reported 20 cases of spontaneous pneumothorax in this hospital in the last ten years. Two of the cases were tuberculous patients. The other 18 cases were nontuberculous on complete study. Since then we have had 2 more cases of spontaneous pneumothorax in healthy individuals. We were able to secure a follow-up on 11 cases and these have all remained nontuberculous. It is interesting that in 6 of the cases negative tuberculin tests were obtained. One of the nontuberculous patients developed a haemothorax. In another case one young man of twenty had an alternating spontaneous pneumothorax. First the spontaneous pneumothorax occurred on the right side and then on the left when the right lung had expanded. Our series of cases confirmed the impression that spontaneous pneumothorax in the healthy is as a rule nontuberculous, that the patients recover within a short time and are none the worse for their experience, and that they can resume their normal activities when the symptoms clear.

However, we feel that, although it is generally accepted that spontaneous pneumothorax may have no tuberculous significance, the aetiology of the condition is still obscure. The most common theories advanced as to the aetiology are: (*1*) infectious, (*2*) congenital, (*3*) emphysematous blebs on the surface of the pleura. The infectious theory can be ruled out by the following facts. First, that there is no pleural reaction. Very few develop fluid and empyemata are almost unknown. The absence of pleural reaction is illustrated by the cases of recurring spontaneous pneumothoraces. Second, that in the idiopathic spontaneous pneumothorax very little treatment is necessary. Whereas, when pneumothorax complicates a pulmonary infection, a tension pneumothorax is often produced which requires immediate decompression.

The second theory, that of congenital origin, appears to have been advanced only because no adequate cause was established for the condition. It is a simple matter to postulate a congenital origin to things that are not understood. The frequency of the accident and the fact that congenital defects rarely occur alone argue against this theory.

The third theory, that of pleural blebs, is the most practicable and most widely accepted theory. A recent observer, Gordon (6) of the Royal Chest Hospital in London, ascribes all cases to rupture of the subpleural blebs. He described 5 cases in whom after reëxpansion he could delineate bullae on the X-ray plate. We were unable to confirm this in our cases. However, we feel that these pleural blebs are the most likely cause. Although we cannot visualize the blebs on the X-ray plate, they are seen commonly enough pathologically. One case in our series, in whom the spontaneous pneumothorax brought on acute cardiac failure with a fatal termination, revealed on postmortem a rupture of a pleural bleb. It would be of interest to do a thoracoscopy in cases of spontaneous pneumothorax to see if a pleural bleb were the cause and to look for the presence of other blebs that might produce the accident in the future.

The origin of these blebs is intriguing. They are evidently areas of localized emphysema, collections of air under the pleura. This air can come only from the lungs. There must occur a rupture of an alveolus or of a terminal bronchiole with the escape of air into the interstitial tissue and producing thereby a localized interstitial emphysema. In this way air can dissect along the septum and reach the pleura causing a localized bulge or a bleb and stretching the pleura over this area. The constant gliding of the parietal over the visceral pleura in this area will gradually thin the pleura over the bleb. With an increase in the tension of the bleb caused by cough or exertion, the bleb may rupture with the escape of air into the pleural cavity. We are told that it requires pressure of from 100 to 300 mm. of water to produce a rupture of healthy lung and pleura. The rupture, therefore, must occur in a weakened area, probably one in which the normal tissue had been destroyed by disease and had been replaced by fibrous tissue which does not stand the strain of overinflation well.

That interstitial emphysema can occur is shown by the following case. (Figure 1.) *E. D.* white female of seventeen was admitted to the Mt. Sinai Hospital, Medical Service No. 1, complaining of sharp pain in the chest and slight dyspnoea. Examination revealed distant breath sounds in the left upper lobe and a diagnosis of spontaneous pneumothorax was made. In a few hours, however, it was noted that there was subcutaneous emphysema above the clavicles. As the X-ray reveals, there is air in the tissues on both sides of the neck and a very slight pneumothorax on the left side. This girl was apparently well until the advent of this condition. There was no history of an injury. The air could have come only from the lungs. The case, therefore, belongs in that group of cases which was discussed by Hamman (7) of Johns Hopkins at the 1937 meeting of the Association of American Physicians, and which he called spontaneous interstitial emphysema. He ascribed the accident to a rupture of the alveolar tissue with the escape of air into the inter-

stitial tissue and its migration along the septa and along the sheaths of the vessels into the mediastinum. In the case of this patient, a small amount of air evidently escaped into the pleural cavity before the vessels entered the hilum.

Hamman, however, was not the first to speak of interstitial emphysema. If we go back to Laennec, we find in his book (1) a complete exposition of pulmonary emphysema. He divided emphysema into two types—the vesicular or pulmonary and the interlobular. On doing postmortem work, Laennec frequently found what he called projections or bulges on the visceral pleura.

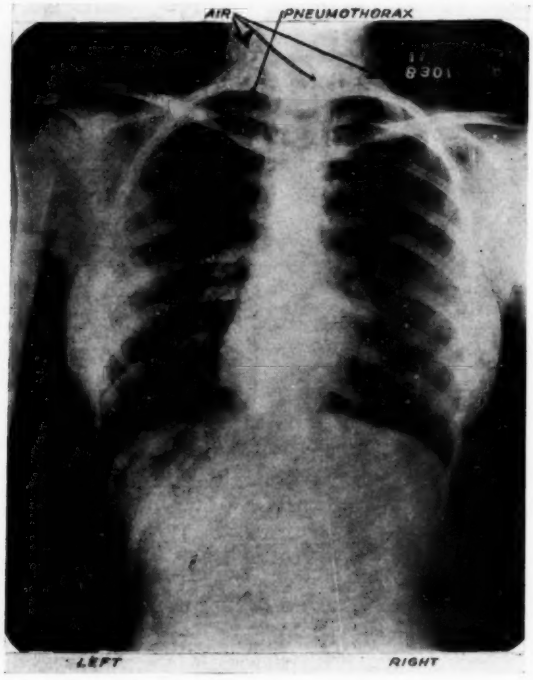

FIG. 1

In true pulmonary emphysema, he tells us, the bulge communicates with a cavity in the viscus, it merely being a continuation of a distended alveolus which bulges on the surface of the lung. Other bulges, however, do not communicate with underlying alveoli and, to differentiate them, he tells us to press the finger over the bulge. If it is due to the first type, the bulge will not move under the surface of the pleura; but if the bulge is due to the second type, it can be made to move by pressing on it with the finger. Laennec also tells us that these blebs are due to rupture of distended vesicles in advanced em-

physema with air passing along the septa to the pleura and causing the emphysematous bleb.

We have then a logical explanation for the production of emphysematous blebs by rupture of which a spontaneous pneumothorax may be caused. We must credit Laennec for the explanation of the cause of spontaneous pneumothorax and spontaneous interstitial emphysema although he did not name them as such.

I wish to thank Dr. Burgess Gordon and Dr. A. I. Rubenstone for use of clinical material.

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STATISTICAL DATA

Edited by JESSAMINE S. WHITNEY

TUBERCULOSIS BED FACILITIES, BY STATES

The revision of the United States Sanatorium Directory in 1938 and the recent receipt of tentative tuberculosis data from the forty-eight State Health Commissioners for the same year furnish figures for the following table showing the provision of tuberculosis sanatorium beds in each state related to the number of tuberculosis deaths for the United States.

Number of beds for tuberculosis cases compared with number of deaths from tuberculosis

STATE	NUMBER OF DEATHS (1938)	TOTAL BEDS* INCLUDING FEDERAL BEDS		TOTAL BEDS* EXCLUDING FEDERAL BEDS	
		Number (1938)	Ratio of beds to deaths	Number (1938)	Ratio of beds to deaths
United States	63,332	89,692	1.4	81,330	1.3
Alabama	1,604	397	0.2	352	0.2
Arizona	862	1,542	1.8	731	0.8
Arkansas	1,003	755	0.8	755	0.8
California	4,033	7,620	1.9	6,817	1.7
Colorado	655	2,613	4.0	2,130	3.3
Connecticut	613	1,676	2.7	1,676	2.7
Delaware	131	224	1.7	224	1.7
District of Columbia	588	923	1.6	900	1.5
Florida	987	869	0.9	862	0.9
Georgia	1,612	650	0.4	641	0.4
Idaho	106	177	1.7	45	0.4
Illinois	3,686	4,644	1.3	4,361	1.2
Indiana	1,380	1,649	1.2	1,649	1.2
Iowa	488	891	1.8	811	1.7
Kansas	428	480	1.1	417	1.0
Kentucky	1,972	1,063	0.5	755	0.4
Louisiana	1,432	799	0.6	659	0.5
Maine	253	574	2.3	567	2.2
Maryland	1,333	1,492	1.1	1,454	1.1
Massachusetts	1,684	4,768	2.8	4,485	2.7

* In addition to beds in sanatoria and preventoria there are included beds in isolation hospitals reporting definite provision for tuberculosis and general hospitals having tuberculosis departments. Beds in mental and penal institutions are *not* included.

Number of beds for tuberculosis cases compared with number of deaths from tuberculosis—Concluded

STATE	NUMBER OF DEATHS (1938)	TOTAL BEDS* INCLUDING FEDERAL BEDS		TOTAL BEDS* EXCLUDING FEDERAL BEDS	
		Number (1938)	Ratio of beds to deaths	Number (1938)	Ratio of beds to deaths
Michigan	1,866	5,035	2.7	4,991	2.7
Minnesota	815	2,579	3.2	2,403	2.9
Mississippi	1,102	522	0.5	522	0.5
Missouri	1,828	2,092	1.1	2,049	1.1
Montana	239	237	1.0	200	0.8
Nebraska	220	268	1.2	243	1.1
Nevada	71	11	0.2	11	0.2
New Hampshire	142**	240	1.7	240	1.7
New Jersey	1,962	3,854	2.0	3,854	2.0
New Mexico	392	1,162	3.0	491	1.3
New York	6,539	13,626	2.1	12,449	1.9
North Carolina	1,876	2,388	1.3	1,659	0.9
North Dakota	136	506	3.7	405	3.0
Ohio	3,090	4,237	1.4	4,062	1.3
Oklahoma	1,162	1,125	1.0	805	0.7
Oregon	305	626	2.1	594	1.9
Pennsylvania	4,348	5,408	1.2	5,266	1.2
Rhode Island	277	728	2.6	728	2.6
South Carolina	917	905	1.0	905	1.0
South Dakota	230	375	1.6	220	1.0
Tennessee	2,180	1,161	0.5	1,161	0.5
Texas	4,119	2,463	0.6	2,124	0.5
Utah	99	48	0.5	48	0.5
Vermont	147	172	1.2	172	1.2
Virginia	1,802	1,329	0.7	1,287	0.7
Washington	718	1,394	1.9	990	1.4
West Virginia	932	820	0.9	820	0.9
Wisconsin	912	2,538	2.8	2,307	2.5
Wyoming	56	37	0.7	33	0.6

** 1937 figure; 1938 data not available.

In this connection a Bill (S. 2547) introduced in Congress June 5, 1939 by Senator Murray of Montana is of interest. The Bill provides an appropriation not to exceed $7,750,000 for the fiscal year ending June 30, 1940; for the following year $33,500,000, and for the third year $37,000,000 and unspecified sums for succeeding years. These sums are to be expended "to establish, extend, and improve measures for the prevention, treatment, and control of

tuberculosis, including the provision of facilities for sanatorium and other care for persons with tuberculosis; for the purpose of making studies, investigations and demonstrations . . . including the training of personnel; . . . and for the printing of reports, documents, and other material. . . ." The Surgeon General of the Public Health Service shall allot these sums to the several states and possessions on the basis of (*1*) population, (*2*) extent of the tuberculosis problem, (*3*) existing facilities for the care of tuberculous patients, and (*4*) financial needs of the respective states. The Bill has been read twice and referred to the Committee on Finance.

WHERE TUBERCULOSIS DEATHS OCCUR

A special report[1] from the Vital Statistics Division of the United States Bureau of the Census, under date of June 14, 1939, gives for the first time for the entire country data concerning deaths in hospitals and institutions and those occurring outside. The figures for tuberculosis are striking. Forty-eight per cent of deaths from tuberculosis, all forms, in the entire United States in 1936 were in "institutions." (By "institutions" is meant not only tuberculosis sanatoria but general hospitals and custodial institutions of all sorts.) The percentages range all the way from 79 per cent in the District of Columbia to 7 per cent in Wyoming.

On first thought we might assume that most of the tuberculosis deaths in institutions would be in tuberculosis sanatoria and hospitals, but the classification according to type of institution does not bear out this assumption. Only 16 per cent of the total tuberculosis deaths were in hospitals or sanatoria exclusively for tuberculosis. The distribution by type of institution is as follows:

TYPE OF INSTITUTION	PERCENTAGE OF TOTAL TUBERCULOSIS DEATHS IN UNITED STATES, 1936, OCCURRING IN SPECIFIED TYPE OF INSTITUTION
All institutions	48.0
General hospital	23.6
Maternal and children's hospital	0.3
Tuberculosis hospital	15.9
Other hospitals	1.5
Nonresident institution	0.5
Mental institution	5.2
Other resident institutions	1.0

[1] Deaths in Hospitals and Institutions.

Probably the fact of greatest concern in the above table is that over one-twentieth of all tuberculosis deaths in the United States occur in mental institutions.

SCHIZOPHRENIA AND TUBERCULOSIS

In a book recently published by Dr. Franz J. Kallmann, entitled *The Genetics of Schizophrenia*, there is a chapter on "The Genetic Relation between Schizophrenia and Tuberculosis." The study is based on 1,087 schizophrenics admitted to the Berlin-Herzberge Hospital between 1893 and 1902, whose clinical records were still available in 1929. Only those cases with a valid diagnosis of schizophrenia in which the onset of the disease antedated the fortieth year of age were included.

The descendants and immediate relatives of this group have been followed through succeeding years in order to find out the incidence of schizophrenia and tuberculosis among them. They included 3,279 parents, husbands and wives; 3,384 direct descendants; 3,920 brothers, sisters, half-brothers and half-sisters; and 2,194 nephews and nieces.

Doctor Kallmann had made a detailed study of these cases over a long period of years while he was in Germany, and a book showing the results of his study was ready for publication when he came to the United States. Since then the book has been translated into English and the results made available to Americans in their own language.

He divided schizophrenics into the four classical categories: hebephrenia, catatonia, paranoid and simple which have distinct differences in fertility and in incidence of taint among their descendants. In the first two groups, hebephrenics and catatonics, which together he calls the nuclear group, the children showed a 21 per cent probability of having schizophrenia and 17 per cent mortality from tuberculosis between the ages of ten and fifty-nine. The other two groups, the paranoids and the simple, which Doctor Kallmann calls the peripheral group, show in the children 11 per cent probability of schizophrenia and 10 per cent mortality from tuberculosis.

The figures above are only for direct descendants in the first generation, namely, children of schizophrenics. For the brothers and sisters and the half-brothers and half-sisters, the corresponding figures are 12 per cent probability of schizophrenia and 9 per cent mortality from tuberculosis. For the grandchildren the respective percentage figures are 4 and 5. For the nephews and nieces the figures are 4 per cent and 7 per cent.

After a thorough discussion of the literature on this subject, the author concludes that the "primary anatomical substratum for the tendency to schizophrenia and the low resistance to tuberculosis, as well as for

the predispositional relationship between these two disease groups, can by no means depend solely on a physical similarity or on specific toxic-endocrine or other organic changes *per se*. Instead, their biological basis must be much deeper sought, probably in a close connection with specific tissue characteristics."

The question of the exact nature of this tissue inferiority can only be answered tentatively at the present.

GRAPHIC TRACINGS OF RESPIRATION IN STUDY OF PULMONARY DISEASE[1]

ANDRE COURNAND, DICKINSON W. RICHARDS, JR. AND ROBERT C. DARLING

The purpose of the present article is to describe a simple and rapid method of graphic registration of breathing, requiring as sole equipment a modified basal metabolism apparatus, and to show the usefulness of this technique in clinical medicine.

The essential features of pulmonary function may be described as: (*1*) air circulation, or the movement of air between the atmosphere and the alveoli; (*2*) diffusion of respiratory gases between alveoli and pulmonary capillaries; (*3*) circulation of blood through the pulmonary vascular bed.

(*1*) That an individual will be physically incapacitated, or *dyspnoeic*, if he cannot ventilate his lungs, is obvious. Yet the importance of the *ventilatory factor* in the symptomatology of cardiorespiratory conditions is probably still insufficiently appreciated among clinicians. By ventilatory factor, we mean that which has to do with the mechanics of movement of chest and lungs.

To state the problem of the ventilatory factor in simple terms: there is for every individual in any given state—rest, exercise, emotional anxiety, disease, etc.—a certain ventilatory or *breathing requirement*. At rest, a man will normally breathe, let us say, 6 litres of air per minute; in a certain degree of moderate exercise, 25 litres per minute; and so forth. If he can provide a pulmonary ventilation of 25 litres per minute, easily and without conscious effort, he will notice no symptoms. In other words, he will not be dyspnoeic. Dyspnoea will appear if the individual's *breathing capacity* does not easily and without effort accommodate his *breathing requirement* for any given metabolic state.

Without attempting any analysis of the very complex neuromuscular regulation of breathing, and its many pathological disturbances, we may point out a few of the simpler forms of pulmonary dysfunction, which

[1] From the Department of Medicine, College of Physicians and Surgeons, Columbia University, the Tuberculosis Service, Bellevue Hospital, and the Presbyterian Hospital, New York City.

lead to the production of dyspnoea by compromising the breathing capacity. Such are: (*a*) partial obstruction of the tracheobronchial air passages, leading to increased respiratory effort, with retardation of breathing; (*b*) reduced capacity of movement of the lungs, as by injury, paralysis, or disease of the osteomuscular framework of the chest, collapse of the lung (pneumothorax, hydrothorax); (*c*) reduced distensibility of the lung, as from vascular congestion (congestive heart failure), or fibrosis.

On the other hand, the breathing requirement may be altered by exertion, increased metabolism, anoxia of blood and tissues, alterations in nervous regulation of breathing from external or internal (reflex) causes.

(*2*) Inadequate aeration of blood by the lungs is ordinarily tested by measuring the oxygen saturation of the arterial blood. It was found some years ago by Uhlenbruck (1), however, that an oxygen deficiency in the blood and body tissues could often be detected through spirographic methods.

In normal subjects at rest, as is well known, the same amount of oxygen is absorbed from the inhaled air per minute, whether this air is atmospheric (21 per cent oxygen) or pure oxygen. In individuals suffering from anoxia of blood and tissues, on the other hand, inhalation of pure oxygen will result in a transitory increase in the absorption of oxygen into the body. This excess oxygen absorbed by anoxaemic subjects during the first few minutes of breathing pure oxygen (or a high oxygen mixture) has been termed by Uhlenbruck the *oxygen deficit.*

MEASUREMENTS

By simple measurements of ventilatory function—form of breathing, maximum depth (vital capacity), maximum volume in unit time, speed (or retardation) of breathing—it is often possible to analyze ventilatory dysfunction and obtain information both as to the nature and the extent of physical disability in any individual case.

The measurements which the method here described provides are as follows:

(*a*) Form of quiet and deep breathing
(*b*) Lung volumes (with the exception of residual air)
(*c*) Breathing capacity, that is, the maximum possible pulmonary ventilation per unit of time
(*d*) The oxygen deficit

In emphasizing the usefulness of the spirographic method, it is important to mention that it provides fixed, objective records for compari-

son during the evolution of chronic pulmonary disease; and for the estimation of the value of therapeutic procedures. It has also been used in problems of compensation in industrial medicine and of disability claims. It has in our practice become a necessary supplement to the routine methods of physical and X-ray examination.

It may be noted that the technique and apparatus described in this paper are a part of a more general and comprehensive method of study of respiratory and pulmonary function, in which we have been interested for some years (2, 3); work which has in great part developed out of the work of Knipping (4), Anthony (5), Uhlenbruck (1), Christie (6), McCann and his associates (7), Hermannsen (8), Nylin (9) and others.

DESCRIPTION OF THE APPARATUS

The apparatus used (figure 1)[2] is a modified recording spirometer of the closed circuit type, derived from the Benedict-Roth apparatus in general use for basal metabolism determinations. The essential features of this apparatus are:

(*1*) A spirometer cylinder of nine-litre capacity
(*2*) Large tubing of one-inch inside diameter and large flutter valves, in order to minimize the resistance in the circuit
(*3*) A motor-driven kymograph, with two speeds, the slow being the same as that of the basal metabolism apparatus of the Benedict-Roth type and the fast, five times as rapid
(*4*) A recording ventilometer (Reichert (10)), recording only (and reducing 25 times) the inspiratory excursions of the spirometer cylinder. This simplifies considerably the computation of results.

In its actual design, the apparatus is of course not ideal. The inertia of the bell and the slight frictional resistance of the recording devices result in a certain decrease in maximum values of ventilation, as compared with theoretical maxima using frictionless apparatus. However, when standard values in normal subjects have been established, the apparatus is adequate for the study of abnormal states.

A few recommendations as to details may be mentioned. Prior to the recording of tracings, the tests should be explained to the patient. He should become familiar with breathing into a closed circuit, and should try to avoid overconsciousness of breathing motions, and yet be

[2] The apparatus was manufactured by Warren E. Collins, Inc., Boston, Massachusetts.

aware of the timing of the different breathing efforts. Standard basal conditions are advisable, though not necessary.

METHODS

Quiet breathing: (figure 2, sections 1 and 2.) The spirometer cylinder is three-quarters filled with room air, and a small extra amount of oxy-

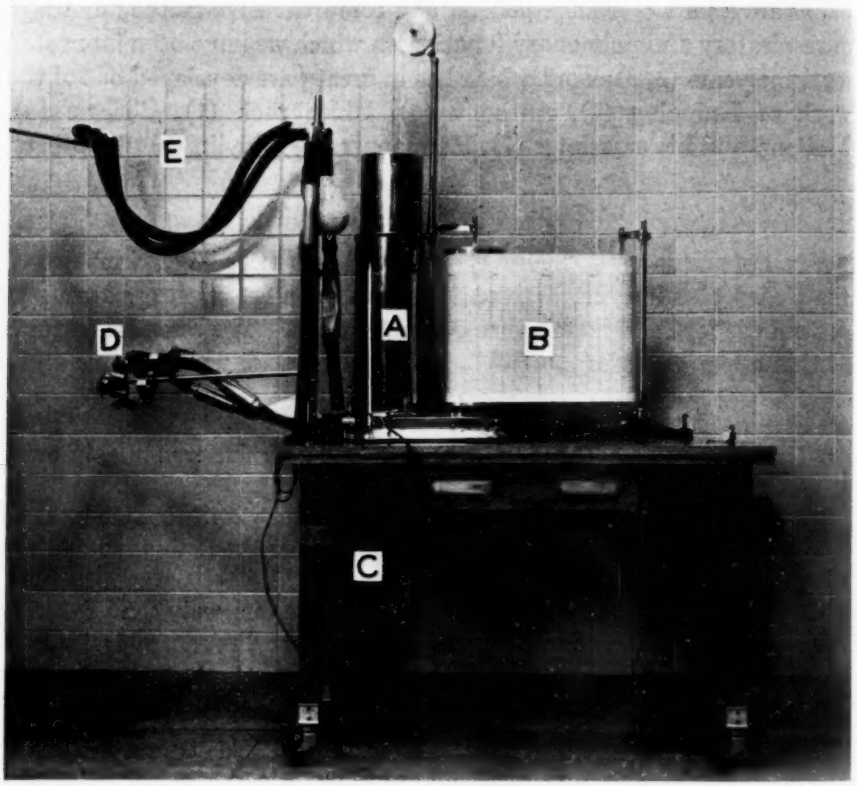


FIG. 1. Photograph and diagram of apparatus. A: Spirometer. B: Recording drum. C: Oxygen tank. D: Mouthpiece, three-way stopcocks, rubber tubing, flutter valves; for use in lung volume determinations and oxygen deficit. The "shutoff valve" (see text) is just above mouthpiece; the "large three-way valve" to the right along upper line of tubing. E: Mouthpiece, large tubing, large flutter valves, for use in maximum ventilation.

gen, about 400 cc., is added. The kymograph is set to run at fast speed. The shut-off valve is turned to the spirometer circuit, and a record of quiet breathing is taken.

Vital capacity: When a satisfactory record of quiet breathing has been obtained, the subject is directed, at the end of a normal expiration, to

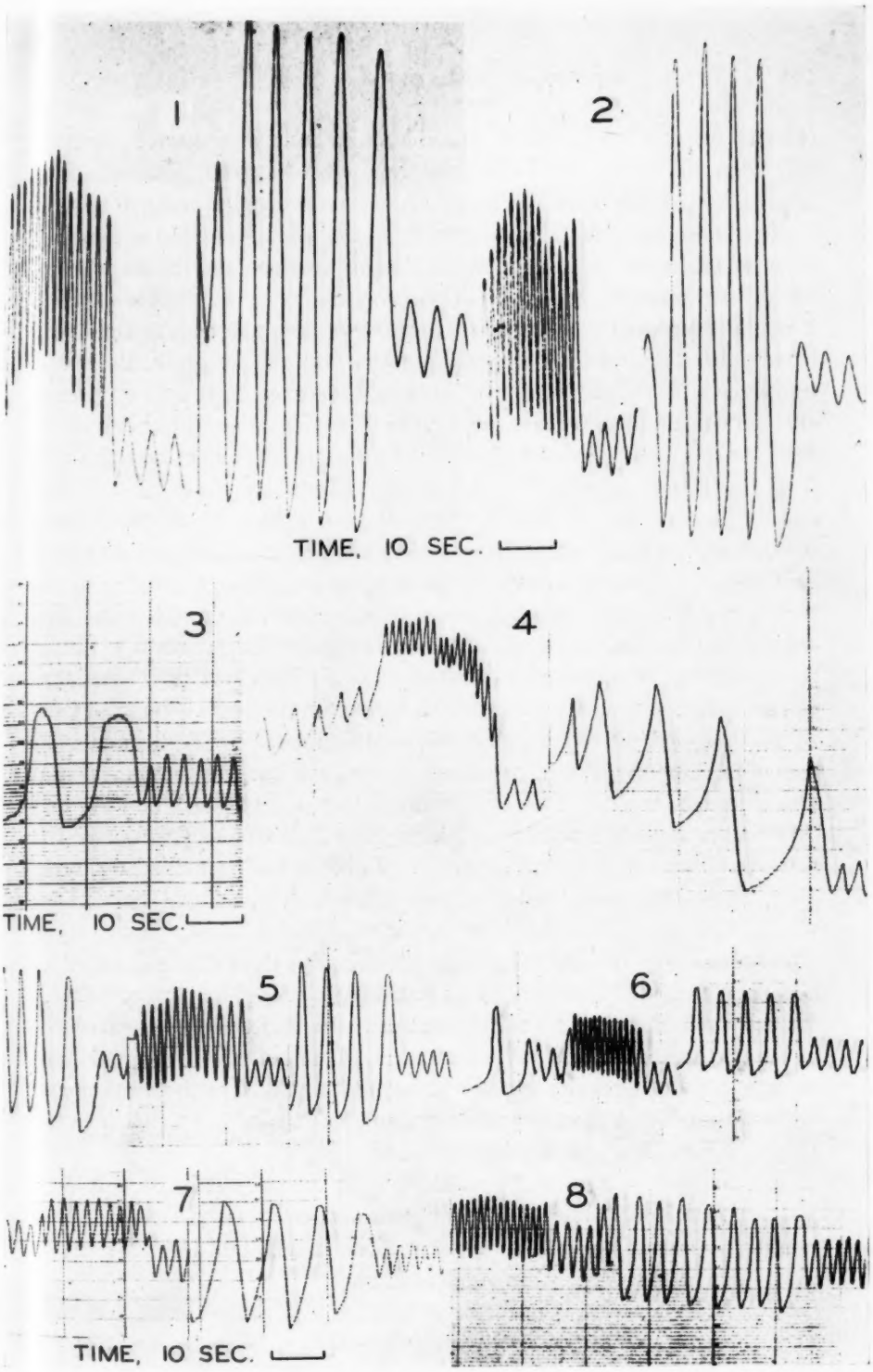


FIG. 2. Spirograms of normal and pathological subjects, in quiet breathing, vital capacity breath, maximal deep breathing, maximal rapid breathing. Tracing reads right to left, inspiration upward, expiration downward. Sections 1 and 2, normal subject; 3, cardiac patient; 4, advanced emphysema; 5, after thoracoplasty; 6, after thoracoplasty; 7, fibrosis and tracheobronchial stenosis; 8, kyphoscoliosis.

take as deep an inspiration as possible, a measure of the *complementary air;* then to empty his lungs completely by forced expiration, thus measuring the *vital capacity*, as this function is usually understood.

Maximum (deep) breathing capacity: At the end of a forced expiration, he is asked to take a succession of deep inspirations and expirations, as rapidly as possible during a period of from fifteen to thirty seconds. This gives a measure of *maximum (deep) breathing capacity*, or the maximum pulmonary ventilation possible when very deep individual breaths are taken. Each breath, according to this technique, is usually a little short of the actual vital capacity (figure 2, sections 1 and 2), depth sacrificed for speed; but it is surprising how consistent a pattern of maximum deep breathing is obtained with normal subjects.

Maximum reserve air plus complementary air: After a rest period of a few minutes, during which the spirometer is refilled with room air and a small amount of oxygen is added, the subject is again connected with the closed circuit. A few normal breaths are recorded and, at the end of a normal expiration, he is directed to continue the expiratory movement, forcing out as much as possible of the air from his chest, a measure of the *reserve air*. This is followed by a maximum inspiration, and then by a succession of deep respirations as described. In the normal individual the reserve air will be essentially the same whether begun at the end of quiet inspiration or expiration (figure 2, sections 1 and 2); and "maximum reserve air plus complementary air" will be practically the same in volume as the vital capacity. In certain abnormal states, however, these two measurements may differ widely, as will be demonstrated below.

Maximum (rapid) breathing capacity: Finally, the subject is asked to breathe "as rapidly and deeply as possible, the most he can ventilate," for a period of fifteen to thirty seconds. In this technique, emphasis is on the greatest speed of pulmonary air exchange. In normal individuals it usually results in amplitude about one-half of the vital capacity, with rates of 40 to 60 per minute; and this technique also brings the largest values for total ventilation.

The measurements may be repeated with the subject in the standing position; the total time of recording should not exceed ten to fifteen minutes. The computation of the records is facilitated by the use of lined graph paper and of the ventilograph.

Oxygen deficit: The spirometer is first almost completely filled with

room air. The oxygen tank is attached through rubber tubing to a special admission stopcock on the expiratory side of the circuit, and 400 c.c. of oxygen admitted into the spirometer (to replace that which is to be absorbed during rebreathing). The connection should be leak-proof, and closed between oxygen refills. The kymograph is moving at slow speed. The subject, in recumbent position, is connected with the spirometer circuit by means of the shut-off valve, and a record of quiet breathing is taken during two minutes. The oxygen percentage will then be still approximately atmospheric, 19 to 20 per cent. At the end of the period, without disconnecting the subject from the circuit, the original level of the tracing is reëstablished by means of admitting a certain amount of oxygen from a tank. With a little experience, it is easy to add an amount of oxygen identical with the amount withdrawn by respiration. Three periods of two minutes each are thus recorded, with repeated oxygen refills and without interruption. The shut-off valve is then turned again to room air. By way of a three-way valve of large bore, placed in the inspiratory circuit (see figure 1), the spirometer cylinder is washed through several times with pure oxygen, without disturbing the patient. The latter is then shifted again to the closed circuit, and three periods of two minutes each of quiet breathing, with intermittent refills of oxygen in the manner described above, are recorded.

The oxygen absorbed is measured, as in the ordinary basal metabolism technique, by the slopes of the tracings. Rate of respiration and total ventilation may also be calculated. As shown in figure 4, section 1, oxygen deficit in normal subjects is zero; whereas in figure 4, section 2, an anoxaemic subject, a marked relative increase of oxygen consumption is noted during the first few minutes of high oxygen breathing as compared with the oxygen consumption during the initial period of air breathing.

RESULTS

(A) *Normal subjects* (figure 2, sections 1 and 2; figure 4, section 1)

(*1*) *Form of the tracings of quiet breathing. Time ratio between inspiration and expiration:* The steepness and the amplitude of inspiratory and expiratory tracings vary considerably from one subject to another, according to the rate and the volume of ventilation per minute. Individual factors are at play here, but the time ratio between inspiration

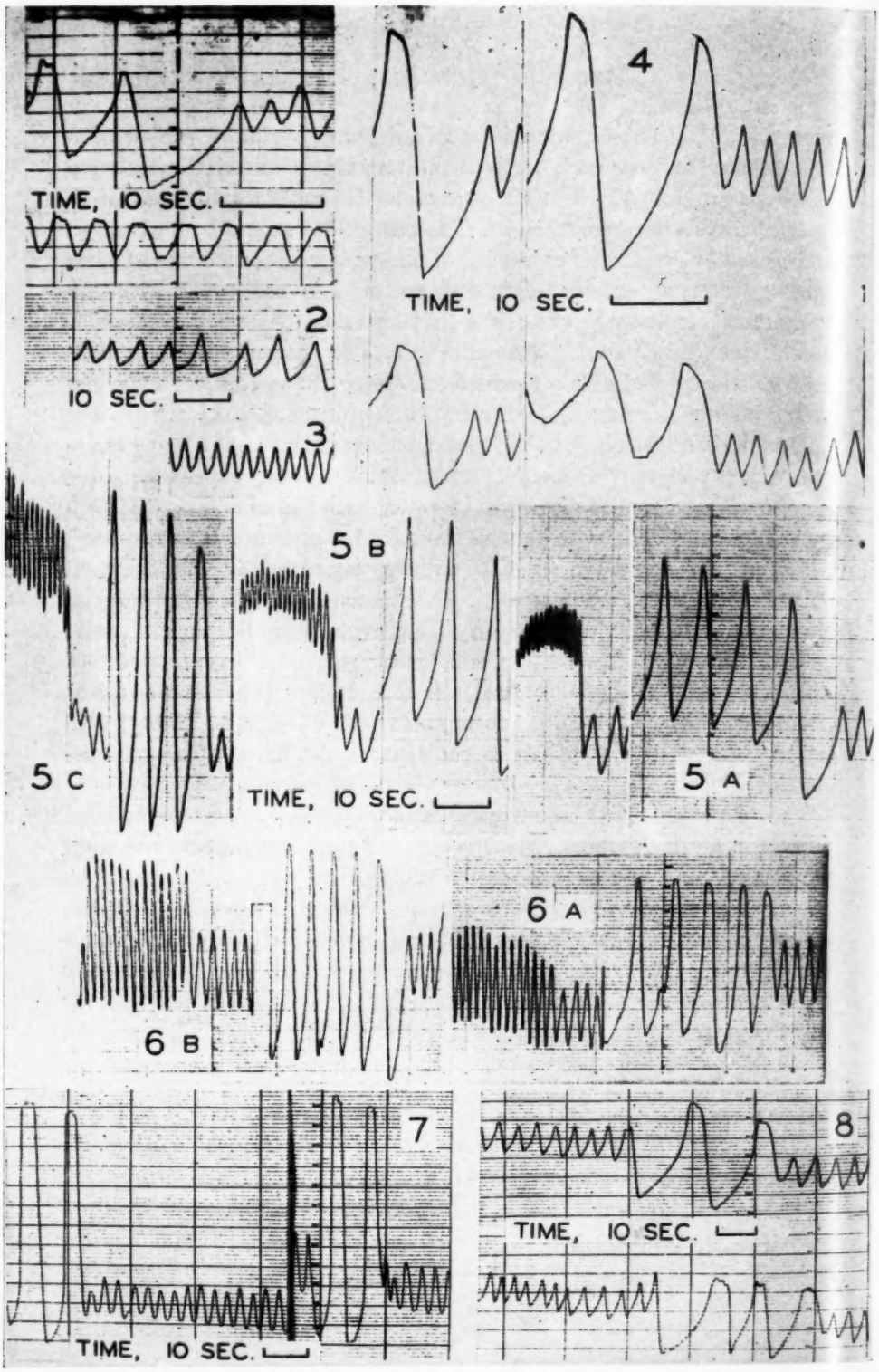


FIG. 3. Pathological spirograms. Section 1, emphysema, deep breathing; 2, emphysema, quiet breathing; 3, after thoracoplasty, quiet breathing; 4, emphysema before adrenalin (lower tracing), after adrenalin (upper tracing); 5 and 6, emphysema before and after bronchodilators (see text); 7, cardiac patient (compensated); 8, combined cardiac and emphysema.

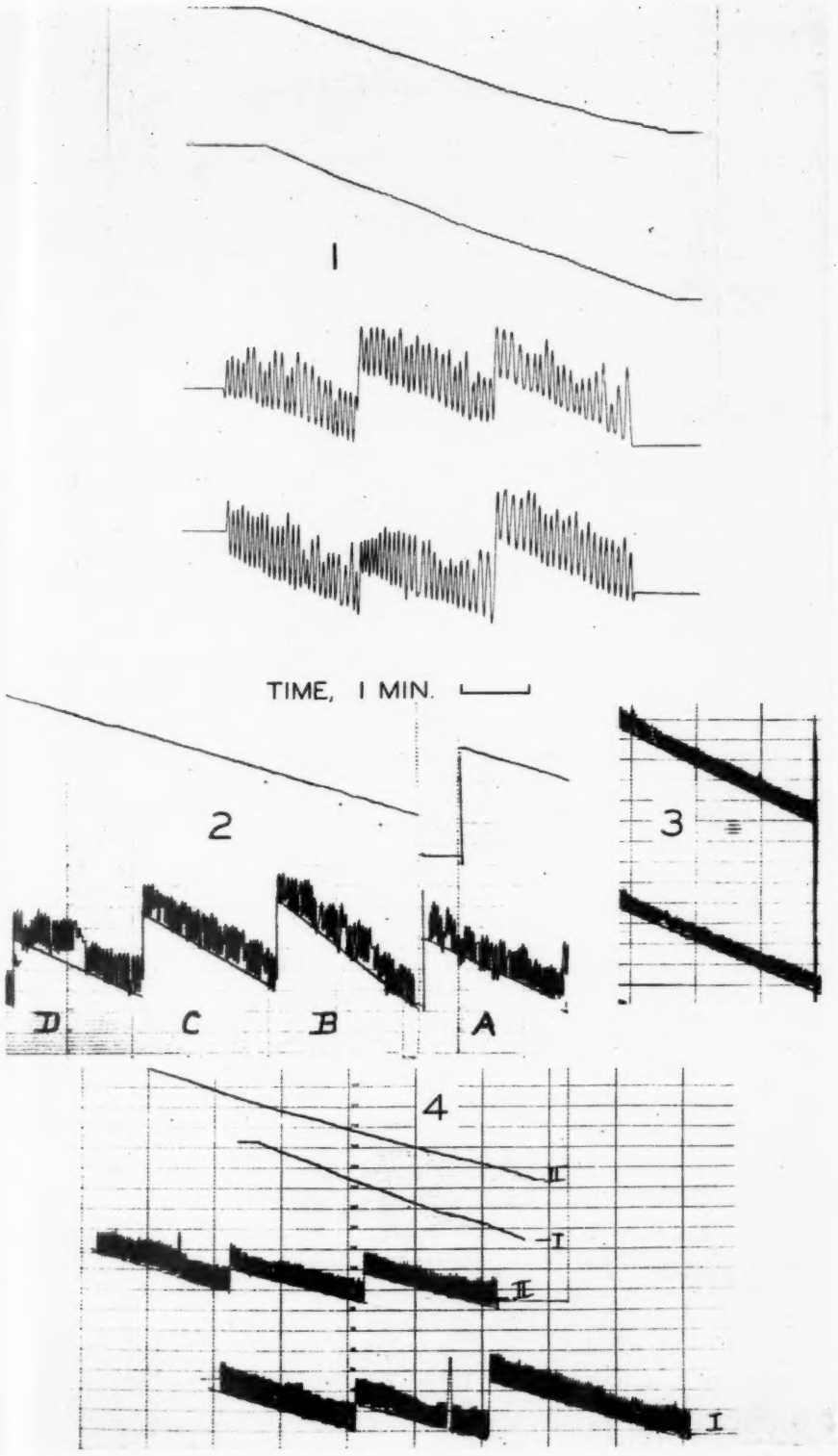


FIG. 4. Oxygen deficit tracings. 1, normal subject; 2, anoxaemic subject; 3, dyspnoeic subject, slight anoxaemia; 4, dyspnoeic subject, not anoxaemic (see text).

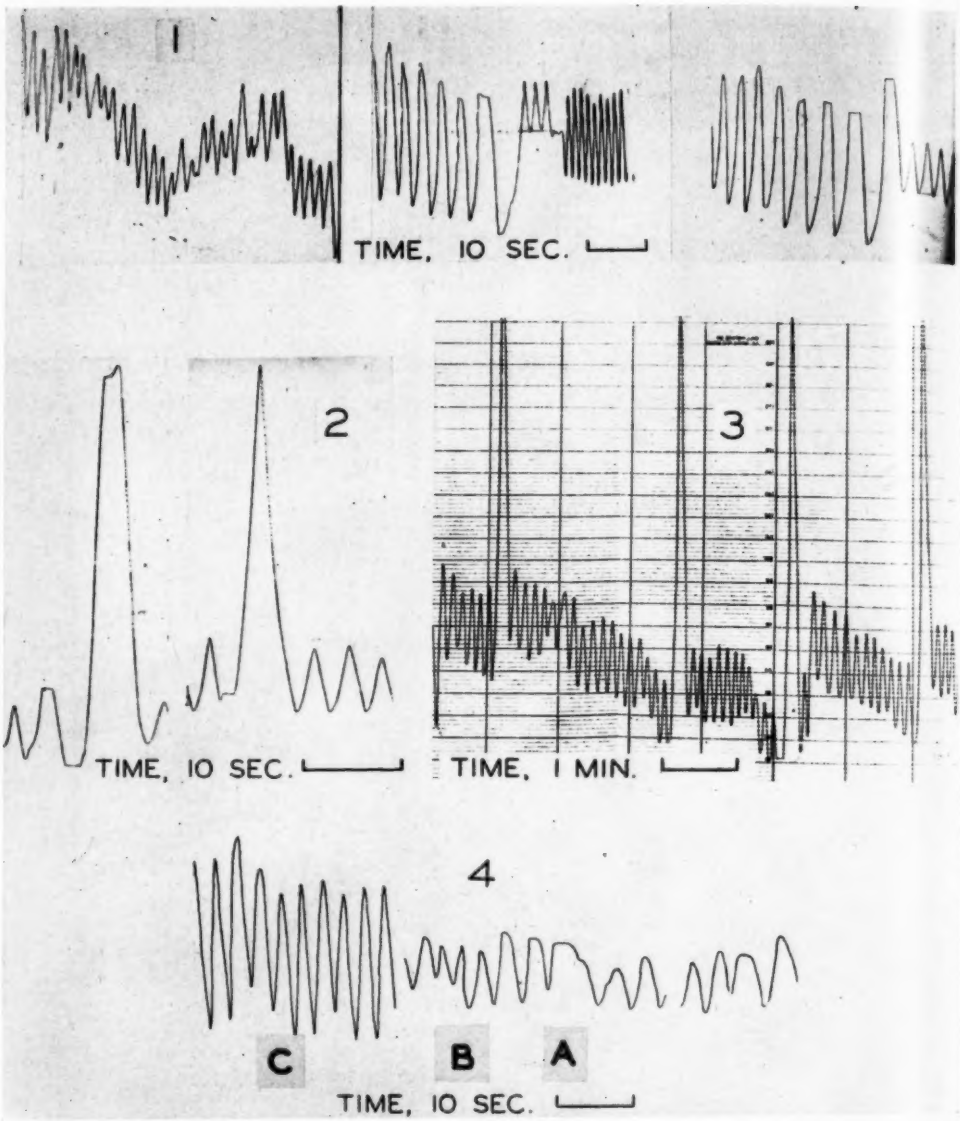


FIG. 5. Abnormal spirograms (see text). 1, nonunion of ribs; 2 and 3, respiratory neurosis; 4, malingering: (a) vital capacity, (b) voluntary maximum breathing, (c) reflex (CO_2) maximum breathing.

and expiration, whatever be the volume, remains an approximately constant value estimated at 1/1.1 by Christie (6), 1/1.34 by Knipping and others (4, 5).

(*2*) *Form of tracings during maximum volume changes:* This is characterized by uniform steepness (speed) of almost the entire span of inspiratory and expiratory tracings.

(*3*) *Vital capacity and subdivisions:* In normal subjects these are essentially the same whether the individual starts with deep inspiration, or deep expiration (see figure 2, sections 1 and 2; table 1). These characteristics of volumetric measurements and of form of tracings are evidence of the maintenance of an even and slight resistance to deformation of the elastic lung, whatever the state of inflation or deflation, and of the free movement of air in the air channels and air sacs.

TABLE 1

Physical characteristics of 20 normal males and 20 normal females

	MALES			FEMALES		
	Mean	S.D.*	S.D. of Mean*	Mean	S.D.	S.D. of Mean
Age (years)	27.90	6.16	1.38	27.15	4.96	1.11
Weight (kilograms)	72.45	9.45	9.44	60.30	8.82	1.97
Height (centimetres)	178.65	9.44	2.11	160.0	15.62	3.50
Vital capacity (cubic centimetres)	4,871	837	187	3,377	530	129

* S.D. = standard deviation; S.D. of mean = standard deviation of the mean. The "standard deviation" may be described by the statement that 66 per cent of all cases in the group will fall within a range defined by the mean plus the standard deviation, on one side; and the mean minus the standard deviation, on the other. A range covering twice the standard deviation on either side of the mean will include 95 per cent of all cases. Thus, in the above table, 66 per cent of vital capacities can be expected to fall within the values (4,871 + 837) and (4,871 − 837); 95 per cent within the values (4,871 + 1,674) and (4,871 − 1,674).

As to the magnitude of the vital capacity in normal individuals, there are of course many extensive investigations in the literature (11, 12, 13, 14); vital capacity correlated with age, surface area, height, weight, stem length or combinations of these. Data on a small group of 20 normal males and 20 normal females, with our technique, are presented in table 1. These values approximate average values in other series and indicate that our technique is comparable to other standard procedures.

(*4*) *Breathing capacity:* The significance of this function is that it provides a measure of the actual maximum performance of the whole bodily apparatus for pulmonary ventilation. It is only in recent years that the importance of this measurement has received deserved attention. Hermannsen (8) made a thorough study of the various techniques

of determining the maximum breathing capacity. Comparing, in normal subjects, the two methods ("deep" and "rapid") that have been illustrated in the preceding section, he concluded that the best results were obtained when the volume of each breath was four-fifths that of the vital capacity. If it is insisted that the amplitude be that of the entire vital capacity, the ventilation per minute is notably lower. This is obvious—the last increment of vital capacity is attained only with undue expenditure of effort and of time.

TABLE 2

Maximum breathing capacity in 20 normal males and 20 normal females

	MALES			FEMALES		
	Mean	S.D.*	S.D. of Mean*	Mean	S.D.	S.D. of Mean
Deep Breathing						
Ventilation, lit./min.	121.0	28.3	6.33	86.80	23.2	5.19
Average volume per breath, cc.	3,855	770	172	2,655	383	86
Fast Breathing						
Ventilation, lit./min.	154.0	30.9	6.9	100.4	16.8	3.76
Average volume per breath, cc.	2,466	568	127	1,676	422	94

* See note under table 1.

TABLE 3

Correlation between vital capacity and maximum breathing capacity in 20 normal males and 20 normal females

CHARACTERISTICS CORRELATED	CORRELATION COEFFICIENT	
	In Males	In Females
Vital capacity and maximum breathing capacity (deep)	+.506	+.634
Vital capacity and average breath volume in deep breathing	+.651	+.831
Vital capacity and maximum breathing capacity (fast)	+.489	+.539
Vital capacity and average breath volume in fast breathing	+.599	+.378

In table 2 are tabulated the mean values of maximum deep breathing capacity and maximum rapid breathing capacity in a group of 20 normal males and a group of 20 normal females. This number is not large, but gives an approximate estimate of normal values of breathing capacity by the technique which we have used. For physical characteristics of the two groups and for meaning of standard deviation, etc. see table 1 and footnote. We have found maximum rapid breathing capacity to be larger than the maximum deep breathing in every instance, the ratio

of the two for the group of normal subjects being 122/100. The average amplitude of each breath in deep breathing capacity was 79.1 per cent of total vital capacity for males, 78.6 per cent for females. The amplitude of each breath in rapid breathing capacity was 50.6 per cent of vital capacity for males, 49.7 per cent for females. This experience thus differs somewhat from that of Hermannsen.

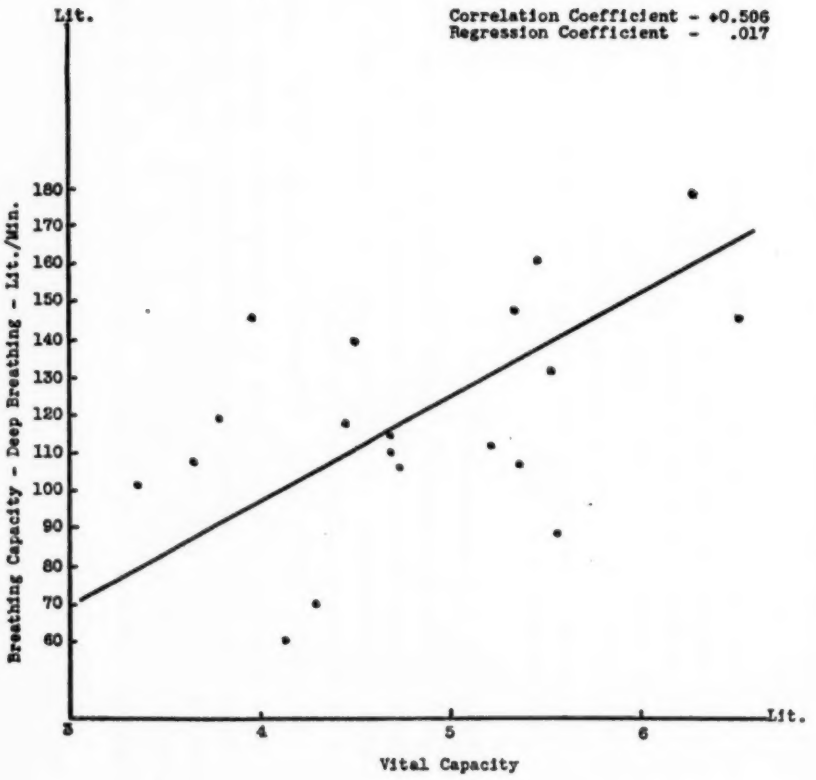
It is of some importance to know how close is the correlation between vital capacity and maximum breathing. Correlation coefficients between these two functions are given in table 3 and figures 6 and 7. For maximum rapid breathing the correlation, though significant, is not high. In other words, there are other factors than vital capacity which determine maximum ventilation. This is what one would expect: maximum ventilation includes the dimension of time and depends upon speed and efficiency of muscular coördination and activity, patency of air passages and other functions not necessarily concerned with the total spatial change in chest volume. Discrepancy between vital capacity and breathing capacity will become more apparent presently, when we consider the breathing in obstructive emphysema and other pathological states.

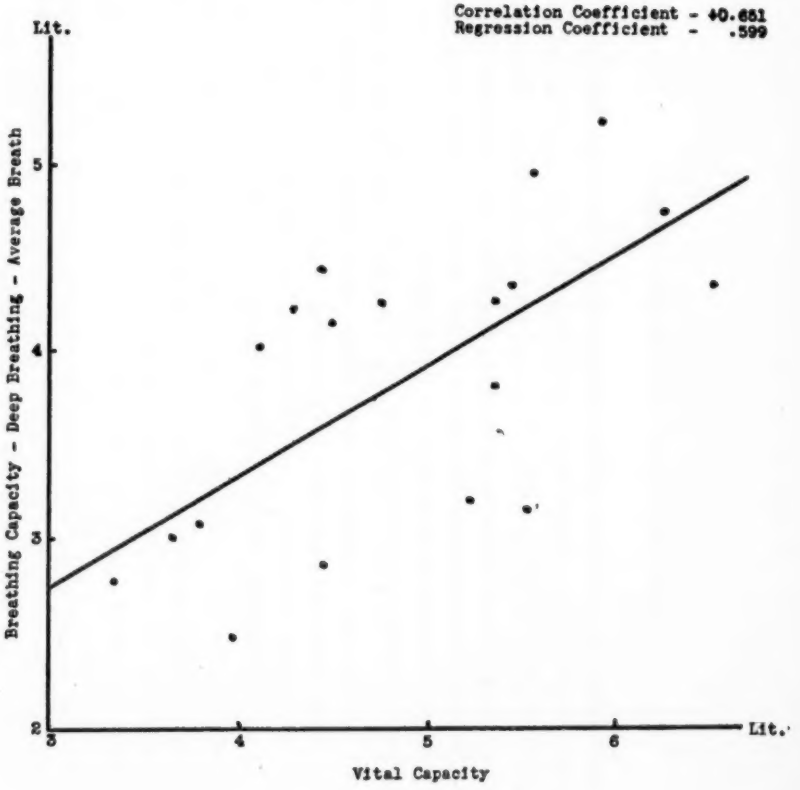
(*5*) *Oxygen deficit:* (Figure 4, section 1; table 2.) In normal subjects, as stated above, the oxygen consumption recorded during quiet breathing remains identical whether the oxygen concentration of the inspired air be that of room air, or higher, up to 100 per cent oxygen. In other words, there is no oxygen deficit. In some instances, the shift from room air to high oxygen breathing is associated in normal subjects with a temporary decrease in rate and in total ventilation per minute (Katz, Hamburger, *et al.* (23)).

(B) *Spirograms in pulmonary disease*

In certain forms of pulmonary disease, both the nature and the extent of abnormality can be quantitatively demonstrated by the spirographic technique outlined above. Illustrative cases, as described below, constitute the major feature of the present study:

(*1*) *Obstructive* (*hypertrophic*) *pulmonary emphysema:* This common condition, occurring, as it does, both as an independent disease and as a secondary phenomenon complicating many other diseases—pulmonary tuberculosis, chronic bronchitis, long-standing asthma, chronic cardiac insufficiency, nontuberculous pulmonary fibrosis—has characteristic spirographic features. One or more of these features can practically


Lit.
Correlation Coefficient - +0.506
Regression Coefficient - .017
Breathing Capacity - Deep Breathing - Lit./Min.
180
170
160
150
140
130
120
110
100
90
80
70
60
3
4
5
6
Lit.
Vital Capacity


Lit.
Correlation Coefficient - +0.661
Regression Coefficient - .599
Breathing Capacity - Deep Breathing - Average Breath
5
4
3
2
3
4
5
6
Lit.
Vital Capacity

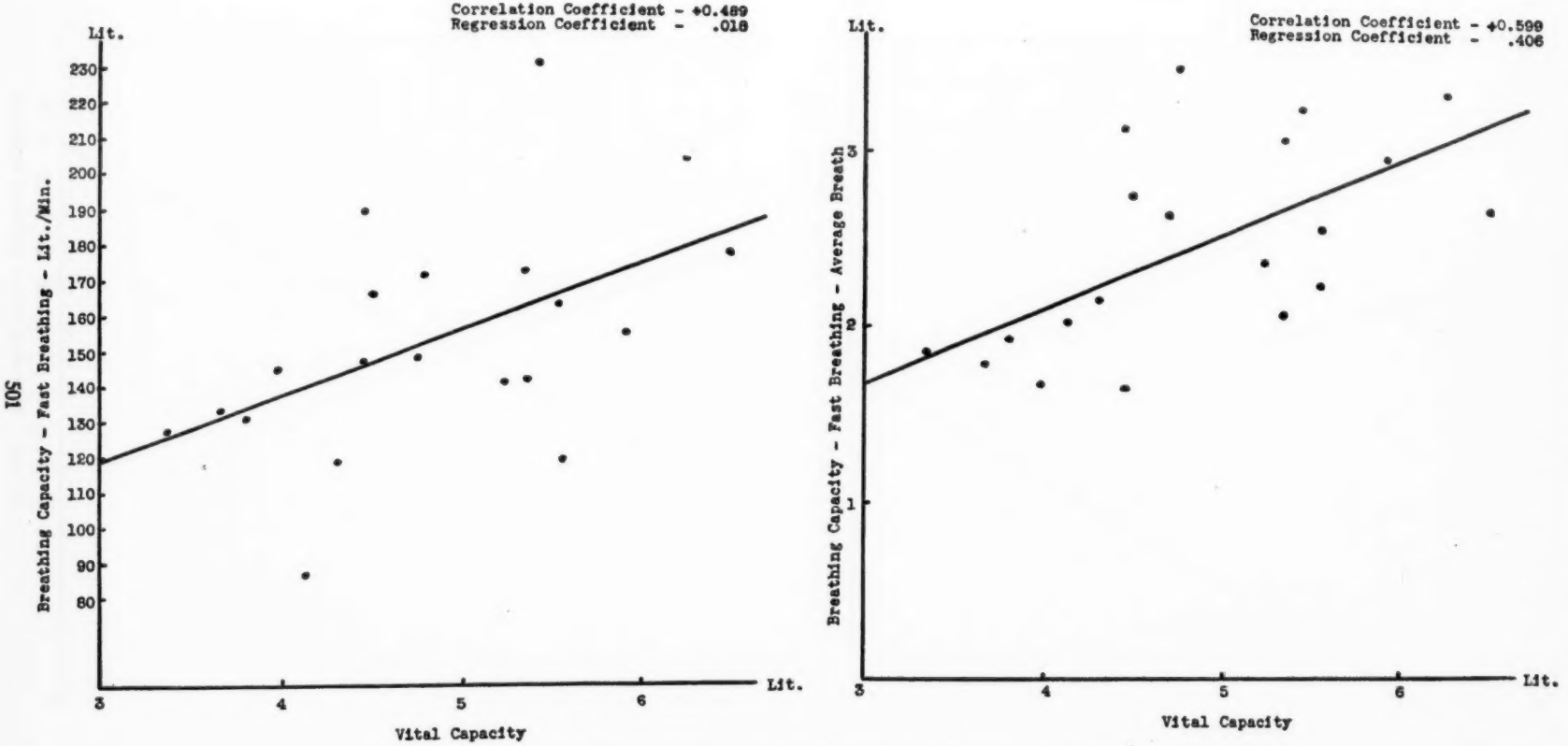
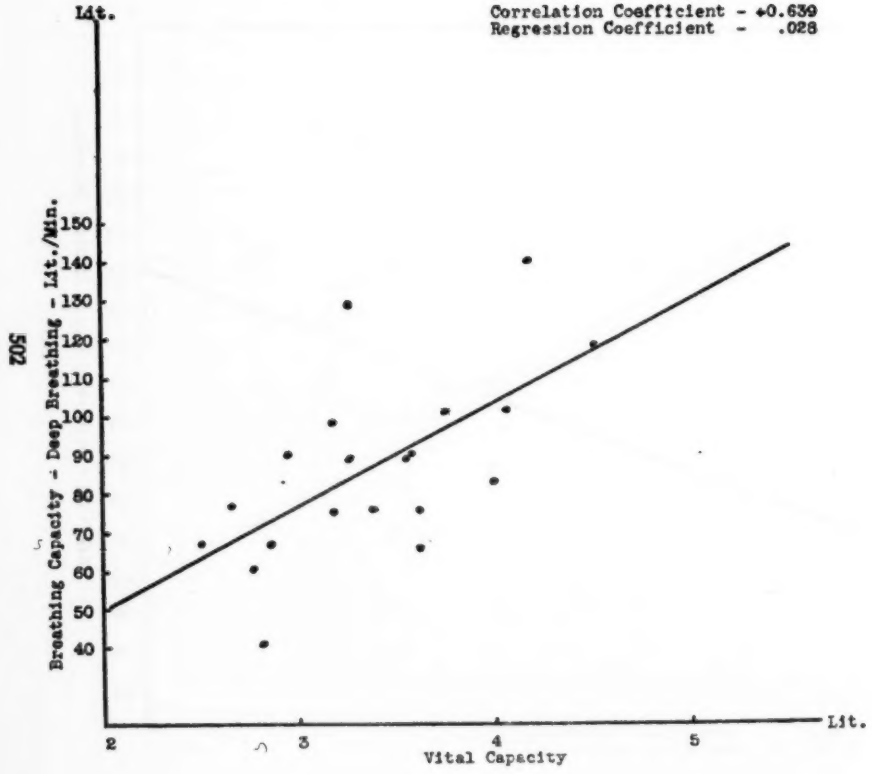
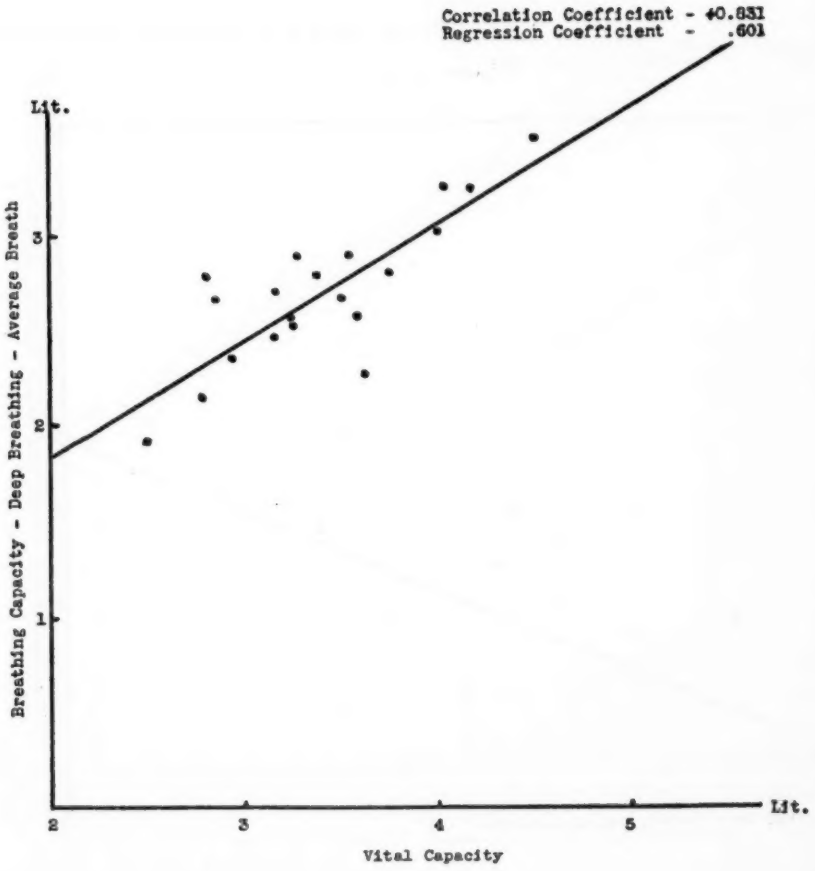


FIG. 6. Correlation between vital capacity and maximum breathing capacity in 20 normal males


Correlation Coefficient - +0.639
Regression Coefficient - .028
Lit.
Breathing Capacity - Deep Breathing - Lit./Min.
150
140
130
120
110
100
90
80
70
60
50
40
2
3
4
5
Lit.
Vital Capacity


Correlation Coefficient - +0.831
Regression Coefficient - .601
Lit.
Breathing Capacity - Deep Breathing - Average Breath
3
2
1
2
3
4
5
Lit.
Vital Capacity

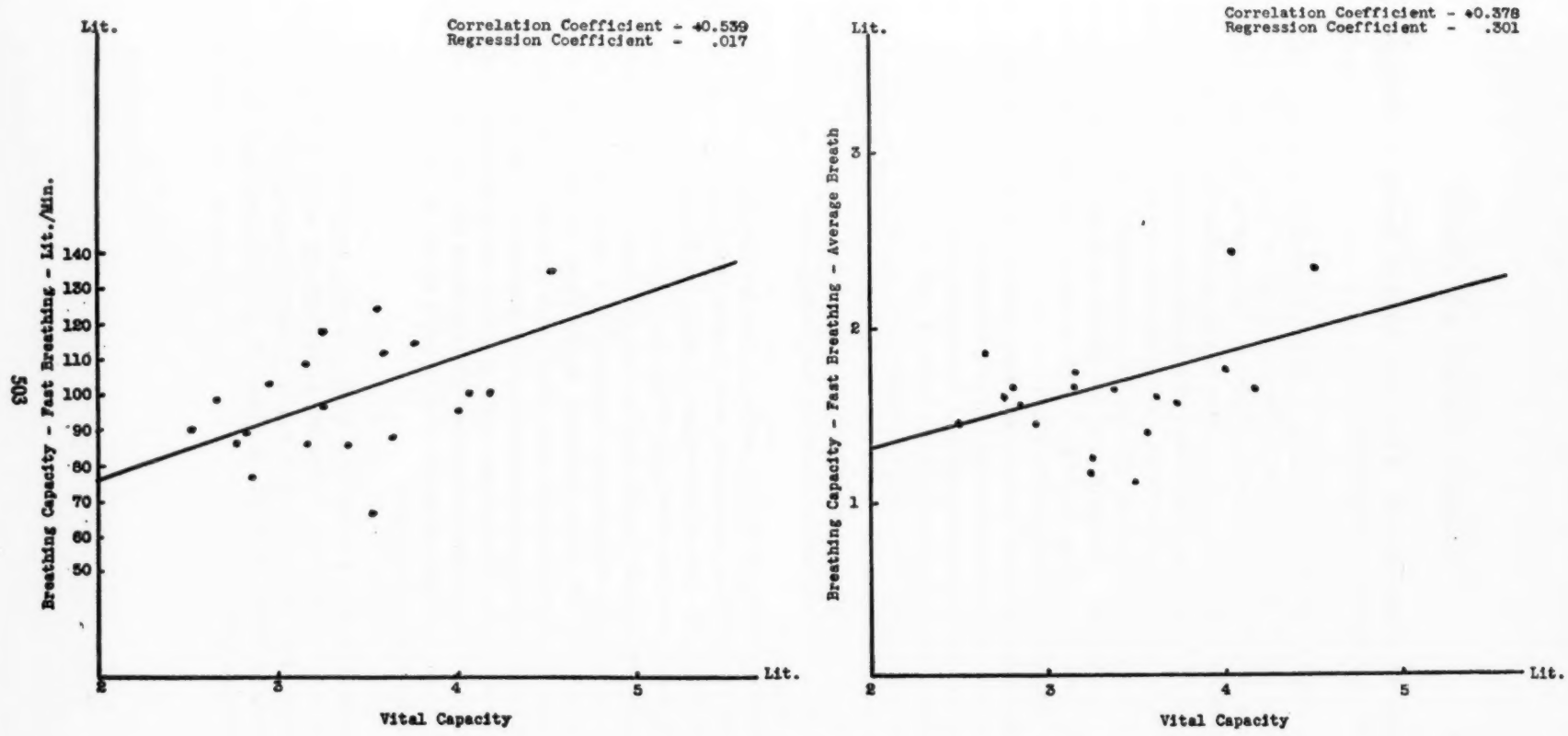


FIG. 7. Correlation between vital capacity and maximum breathing capacity in 20 normal females

always be demonstrated. There are varying degrees of abnormality of the spirogram in emphysema.

Two tracings reproduced in figure 3, section 1, are from a patient with advanced obstructive emphysema. He was a man of fifty-four, who had had chronic sinusitis with asthmatic attacks for many years; his chief complaint was labored respiration, with variable attacks of asthmatic dyspnoea at rest and on mild exertion. His chest conformation was typical of advanced emphysema, in an asthenic subject, with long chest, marked kyphosis, atonic abdomen, persistent contracture of accessory inspiratory muscles. His heart was not enlarged. Venous pressure was 20 mm. of water. Intrapleural pressure in quiet respiration was +10, −5 cm. of water. Arterial oxygen saturation varied between 78 and 88 per cent.

The upper tracing of figure 3, section 1, shows a few quiet respirations (at right), then deep expiration (reserve air), followed by a maximal inspiration and a second maximal expiration. The striking contrast between this and a similar normal tracing (figure 2, sections 1 and 2) is apparent: (*a*) the extreme retardation of breathing especially in the expiratory phase; (*b*) greatly decreased vital capacity (1,420 cc.); (*c*) inability to return to previous expiratory level after a deep inspiration. This latter feature has been noted by Christie and ascribed to overdistention of a lung which has lost its elasticity (retractibility).

The lower tracing in figure 3, section 1, from the same patient, shows certain further abnormalities that appear even in quiet breathing in extreme cases of emphysema: (*a*) marked retardation of entire respiration; (*b*) near the end of inspiration, further retardation ending in a "plateau;" (*c*) at the beginning of expiration, the slope of the tracing is at first steep; (*d*) in many instances, at different levels, expiration is interrupted by a plateau followed by an increasing retardation of the downward tracing to the end of expiration. This tracing very simply records what direct and fluoroscopic examination revealed, namely, an enormous muscular effort, inspiratory as well as expiratory, to counterbalance the lung's lack of distensibility and retractibility, a marked incoördination of respiratory movements (Cournand (2)); in other words, an inadequate correlation between the volume of air moving in the lungs and muscular effort of breathing.

In figure 3, section 2, is shown a tracing of quiet breathing in another case of advanced emphysema, illustrating particularly the aspect of prolonged expiration. By contrast, figure 3, section 3, shows the quiet regular respiration in a case of greatly decreased vital capacity (postthoracoplasty), but with no obstructive element.

Figure 3, section 4, demonstrates another interesting feature of many cases of obstructive emphysema. The patient was a man of fifty-six, with advanced long-standing emphysema. The lower tracing, showing quiet and deep breathing, includes most of the features seen in section 1, though to a less extreme degree. The upper tracing is from the same subject on the same day, taken forty-five minutes after an injection of 1 cc. of epinephrin. It will be noted that the vital capacity is greatly increased, the speed of breathing increased, and the patient can now expire to the same depth, after a complete inspiration, that he can at the end of a normal expiration. In other words, even at this chronic stage, the obstruction can still be relieved to a considerable degree by a bronchodilator drug. This point has been emphasized in recent years by Kountz and Alexander.

It should be noted also that the effect of epinephrin on completeness of expiration suggests a different explanation than that offered by Christie (15): that is, if the retractibility of the lung can be restored by epinephrin, it is probable that the loss of retractibility was due to bronchiolar obstruction (with air trapped beyond the closed bronchioli), rather than to an irreversible loss of elasticity due to connective tissue infiltration and replacement.

The effect of bronchodilators will be further illustrated in the next case selected, that of a man of forty, *M. K.*, with a typical history of Ayerza's syndrome. The sequence of events and the clinical picture fitted remarkably the original description of Ayerza: a history of chronic bronchitis for ten years; dyspnoea on exertion for nine years; development of cyanosis and polycythaemia at about the same time; then appearance of dependent oedema at intervals for four years. When the patient was first examined, he presented evidence of cardiac failure with marked oedema, enlargement of the liver, venous pressure at 160 mm. All this receded rapidly on bed-rest, digitalis and oxygen by nasal catheter. At the time tracings were first taken he had recovered from this recent episode of cardiac failure. Venous pressure was 50 mm. of water. Arterial oxygen saturation varied between 61 and 78 per cent of maximum capacity; red blood cells were 8,400,000, and haemoglobin was 21.7 g. Plasma volume was 2,760 cc., 44 cc. per Kg. body weight (Gregerson); haematocrit 71 per cent.

Figure 3, section 5a, shows a state of moderate obstructive emphysema, with retarded expiration, decreased vital capacity, inability to return to complete expiratory level after a deep inspiration.

The extent of physical disability can be quantitated, in some measure, by use of the maximum breathing capacity, "deep" and "rapid." These are shown graphically in section 5a. It will be noted how, in maximum deep

breathing of the emphysematous subject, the deep capacity breaths are retarded; and how, in maximum rapid breathing, the amplitude of each breath is small and carried out, very rapidly, in the extreme inspiratory position. The figure for maximum deep breathing in 5a is 12.0 litres per minute; for maximum rapid breathing 24.0 litres.

Section 5b of figure 3 shows how a moderate improvement may occur in maximum breathing capacity by use of a bronchodilator inhalation spray. This technique has been described elsewhere (16). In this case a 1 per cent solution of neosynephrin hydrochloride was used, whose action is chiefly that of a local vasoconstrictor, shrinking swollen mucous membranes. Section 5c shows a very much greater increase in breathing capacity in this subject, after hypodermic injection of 1 cc. of 1:1000 epinephrin, the maximum rapid breathing capacity increasing almost three-fold over the resting state. Arterial oxygen saturation was also improved in this instance. The patient has subsequently improved on maintenance dosage of "Vaponefrin" vapor spray.

A similar case of emphysema, though less marked, with a definite improvement in maximum breathing capacity following injection of epinephrin, is illustrated in figure 3, sections 6a and 6b. Maximum deep breathing capacity increased from 16 to 36 litres per minute, maximum rapid breathing capacity from 44 to 64 litres per minute. This patient recovered moderate ambulatory activity on twice-daily injections of epinephrin.

One further measurement is not infrequently significant in advanced emphysema, and that is the oxygen deficit. The patient with Ayerza's syndrome gave an excellent example of this, as shown in figure 4, section 2.

In this patient, as has been mentioned, arterial oxygen saturation was low, on one occasion as low as 61 per cent. In the test of oxygen deficit it was found that, during the first two minutes of high oxygen breathing (b), oxygen consumption was almost twice as large as in room air breathing (a); in each of the next two minutes (c), it was still 80 cc. larger; then it returned to the room air level during the fifth and sixth minutes (d). The figures are given in table 4.

We can summarize briefly the alterations in the spirogram that are found in obstructive emphysema:

1. The most constant, in emphysema of all degrees of severity, is the retardation and prolongation of expiration, becoming more marked as expiration proceeds. In mild cases this is seen only in deep breathing; in advanced cases in quiet breathing also.

2. Inability, on successive deep (vital capacity) breaths, to return

TABLE 4

Data on oxygen deficit determination in seven subjects

NAME	FIGURE	DIAGNOSIS	ARTERIAL BLOOD O_2 SATURATION	RESPIRATION, RATE/MIN.				VENTILATION, LIT./MIN.				O_2 INTAKE, CC./MIN.			
				Room-air	High O_2 concentration			Room-air	High O_2 concentration			Room-air	High O_2 concentration		
				Low	High	0-2 min.	2-4 min.	4-6 min.	Low	High	0-2 min.	2-4 min.	4-6 min.	Low	High	0-2 min.	2-4 min.	4-6 min.
			per cent															
B. K.	4 (1)	Normal subject	96	10	13	10	11	12	5.8	6.0	4.3	5.4	5.7	280	322	322	303	280
M. K.	4 (2)	Ayerza's syndrome	61	18	18	16	16	16	5.3	5.3	5.5	5.2	5.4	275	275	515	355	280
S. B.	4 (3)	Advanced pulmonary tuberculosis	88	34	35	24	29		5.4	5.4	4.7	5.2		265	265	325	325	
M. B.	4 (4)	Chronic pulmonary tuberculosis	97	22	24	21	23	23	5.9	6.9	4.8	4.8	5.9	194	215	194	183	206
P. L.	2 (6)	Chronic pulmonary tuberculosis	94	17	17	17	17	17	3.8	4.3	4.3	4.3	4.1	185	217	207	174	174
H. T.	3 (6)	Fibrosis and emphysema	94	11	12	12	12	11	9.6	9.6	8.4	8.6	8.9	232	250	232	232	240
H. Ba.	5 (1)	Chest deformity	98	21	25	26	23	24	6.7	7.0	6.8	6.8	6.8	190	190	180	180	180

to the same initial expiratory position; corresponding with this, a greater reserve air, when starting from normal expiration, than when starting from full inspiration.

3. Decreased maximum (rapid) breathing capacity, with very small amplitude per breath, and maintenance of extreme inspiratory chest position during this procedure.

4. Improvement, which may be moderate or very marked, in each of 1, 2, 3 above, upon the administration of bronchodilator drugs by spray or injection.

5. In advanced cases, irregular jerky respirations and tracings, associated with poorly coördinated, asynergic respiratory movements.

6. Oxygen deficits, in advanced cases with arterial anoxaemia.

(*2*) ***Pulmonary fibrosis; obstruction in larger bronchi:*** Figure 2, section 7, illustrates a different form of obstructed breathing.

This patient was a woman of forty-two, with wide-spread advancing pulmonary tuberculosis of the fibrocavernous type. She suffered from extreme dyspnoea, aggravated by paroxysmal cough. Respirations were labored and strident. The tracings show a retardation of both inspiration and expiration, with complementary air more diminished than reserve air. Bronchodilator drugs brought no significant increase in speed or capacity of breathing. Bronchoscopy showed findings consistent with the type of the spirogram, namely an extreme, rigid, concentric narrowing of the larger visible bronchi on both sides.

(*3*) ***Congestive heart failure:*** It has been known for many years that congestion of the pulmonary vascular bed, in left-sided heart failure, decreases vital capacity and breathing capacity. According to Christie and Meakins' recent experimental work (17), distensibility of the lung is decreased proportionally to the state of congestion, but retractibility only to a smaller degree; that is, the lung can be expanded only to a limited extent, but returns on expiration to its former position. Decrease in vital capacity, often a proportionally greater decrease of reserve air, some general slowing of the final 100 or 200 cc. of deep inspiration, and similarly of the latter part of deep expiration, are the chief qualitative changes of tracings in pulmonary congestion due to cardiac failure. There is not the progressive retardation during expiration seen in emphysema. These features are illustrated in the tracings of a patient with congestive heart failure (figure 2, section 3).

A similar test, but taken during recovery of compensation, is that of *L. O.*, a man of sixty-three, with arteriosclerotic heart disease and coronary sclerosis. His tracing, figure 3, section 7, shows some limitation of volume of vital capacity (2,590 cc.) especially of reserve air, but no qualitative changes of any significance. To the right of the illustration, vital capacity has been recorded immediately before an infusion test (18); to the left, after the 1,500 cc. of saline were infused within thirty minutes' time. The volume remained the same in both tracings, that is, no further pulmonary congestion developed (see Chamberlain, *et al.* (19)).

By contrast with these two cases, figure 2, section 4, shows a typical record of maximum rapid and deep respiration in a patient with advanced obstructive emphysema.

One of the most important problems encountered in the treatment of cardiac patients is the question of an accompanying chronic pulmonary fibrosis and emphysema with secondary symptoms from this cause. Whether the association of pulmonary emphysema with cardiac failure inducing pulmonary congestion is coincidence, or whether it is brought about by the overdistention of peripheral alveoli, as a result of lung stiffening (Christie (15)), is debatable. In any case, the recognition of obstructive emphysema in such cases may be of practical importance.

Figure 3, section 8, illustrates a case of this kind. The patient, *E. T.*, was a woman of forty-eight, with hypertensive vascular disease, cardiac hypertrophy, coronary arteriosclerosis, and evidence on admission of congestive heart failure. X-ray films of the chest showed some areas of translucency at the right base, which suggested bullous emphysema. Tracings taken at the time the patient had partially recovered compensation confirmed this diagnosis. It will be seen in the tracing that there is a marked retardation of expiration, which occurs not only in deep breathing, but in quiet respirations as well; a very different form of tracing from those of the other cardiac patients just described. It will be noted also that vital capacity is very small, 1,200 cc. (in the upper tracing). It was suspected that this low figure might be due in part to pulmonary fibrosis and in part to chronic passive congestion. Further evidence for the latter was provided by the infusion test (19) (vital capacity and venous pressure measurements after a 1,500 cc. intravenous infusion). The lower tracing, taken after this infusion, shows a vital capacity of only 870 cc., due to increased pulmonary congestion produced by this procedure.

It will be clear from the above observations how large a factor the loss of breathing capacity may become in the causation of cardiac dysp-

noea. The oxygen deficit may also be large in some cases of congestive heart failure.

(*4*) *Chest deformities:* A structural deformity of the chest may be an important cause of physical disability, especially in contributing to the phenomenon of dyspnoea. Again the problem is whether the breathing capacity is reduced, or the breathing requirement increased, or both.

In defining and evaluating these factors, the spirogram may be of considerable assistance.

H. S., a female of twenty-one, provides an illustration (figure 2, section 8). Her complaint was dyspnoea on exertion. She had a fairly marked kyphoscoliosis, of rachitic origin, and a typical pigeon breast. She was a nervous individual, and was obviously hyperventilating at the time of observation to such an extent that she developed signs of tetany. Her spirogram shows the following characteristics: (*a*) Lung volumes considerably and uniformly decreased, with a vital capacity of 1,120 cc., reserve air 260 cc. (*b*) On the other hand, there is no significant retardation of respiration, either in inspiratory or expiratory phase. Thus there is nothing to suggest obstructive breathing of the emphysematous type. (*c*) Injection of a bronchodilator drug (1 cc. of 1:1000 epinephrin) produced no change in lung volumes. (*d*) Quiet breathing (at right of tracing) demonstrates hyperventilation at rest. (*e*) Breathing capacity is much decreased, corresponding with the decreased lung volumes. Maximum deep breathing capacity is only 15.2 litres per minute, maximum rapid breathing 29.5 litres per minute. Thus in this subject dyspnoea is due primarily to limited ventilatory capacity due to structural loss of amplitude of breathing. Nervous hyperventilation may be a contributory effect.

It should be noted that the spirogram does not identify the presence of localized emphysema, if there is no diffuse obstruction of air passages; such localized lesions as Loeschke describes in these cases of kyphoscoliosis.

Figure 2, section 5, is the spirogram of *M. B.*, a woman of twenty-eight, four months after a successful thoracoplasty, at which four upper ribs were removed. In addition, she had a kyphoscoliosis from a healed tuberculosis of the spine. The spirogram shows the usual change seen after uncomplicated thoracoplasty: small tidal air, considerable decrease in lung volumes, but without qualitative change in form of breathing. The tracings are, in fact, quite similar in form to those of normal individuals (figure 2, sections 1 and 2), but much smaller in amplitude. With breathing capacity thus limited, dyspnoea will naturally be expected beyond a certain limit of moderate exertion, but will not occur at rest or on slight exertion.

Figure 4, section 4, is a tracing of oxygen deficit from the same subject. As seen, there is no oxygen deficit; an observation consistent with the finding of normal arterial oxygen saturation (95 per cent).

The next case illustrated (figure 5, section 1) is of great interest from the point of view of the spirogram. *F. Ba.*, a man of forty-four, a steam locomotive engineer, had suffered a crushing injury, following derailment and overturning of a locomotive, resulting in a fracture of the sternum, and fracture of five ribs on one side and six on the other. Nine months after apparent consolidation of the rib fractures, he had been referred to us for evaluation of cardio-respiratory status. He suffered from moderate exertional dyspnoea. His chest anteriorly was flattened, due to his injury, and the sternum was depressed inward.

The spirogram (figure 5, section 1, right hand tracing) shows normal quiet breathing, and a vital capacity tracing of fair volume, though complementary air is considerably reduced. Maximum rapid breathing (right half of middle tracing) is decreased (48 litres per minute), but only moderately. The striking defect in this patient's spirogram is brought out when he makes a maximal expiration and then attempts to inspire completely. As shown in the middle tracing, after this complete expiration he is unable to fill his lungs even to the level of previous quiet breathing; and only gradually does his capacity to inspire deeply return to its previous level.

Careful study of the chest revealed the cause of this defective breathing, in that there was no bony union of the fractured ribs on either side. The anterior chest was a movable placque, tending to be held backward on deep inspiration, and being only slowly pulled out anteriorly as the fibrous unions of the ribs gradually contracted to their resting positions. A further evidence of irregularity of respiration produced by this movable anterior chest wall is shown by the great variability in mean chest position during quiet breathing (left hand tracing, section 1).

The only cure for this type of pulmonary dysfunction would obviously be an operative fusion of the fractured rib ends.

(*5*) *Respiratory neuroses:* Breathing pattern has become of increasing interest to neurologists and psychiatrists. Spirograms have been used for many years in the study of respiratory disturbances observed during such diseases as *encephalitis lethargica*, or with lesions of the floor of the third ventricle, to mention only the most interesting (P. Marie and G. Levy-Jelliffe); but it is only recently that, in well recognized psychiatric entities, this method of study has received attention (Thomson and

Corwin (20)). Christie in a recent publication (21) has described various forms of respiratory tracings and correlated them with different types of neurosis. An extensive bibliography on this subject is given by Caughey (22).

One of these types, classified by Christie as a form of "conversion hysteria" is interesting in several respects. The presenting symptom in this group is dyspnoea. It is essentially characterized by recurring deep sighing respirations associated with the feeling of inability "to pull the air through." It occurs at rest as well as during exertion. The frequency of occurrence of the sighing respirations varies in different patients, and in the same patient under different conditions, sometimes quite infrequently during the day, sometimes several times in a minute. Often several sighs are taken before the patient experiences one which gives "satisfaction." Figure 5, section 3, illustrates this type of breathing. A background of vagal hypertonia is often observed in these patients, such as slow pulse and spastic colon. Figure 5, section 2, gives the spirogram of this patient, on a rapidly moving drum. The curve on the right gives the deep sigh, showing the relatively slow beginning of the movement, accelerating as the inspiration proceeds, followed by a rapid unimpeded expiration. The tracing on the left, for comparison, is a voluntary maximum inspiration by the same patient.

Other forms of respiratory neurosis have been described and are discussed in the references given above.

(*6*) *Malingering:* Respiratory tracings sometimes can serve to prove malingering on the part of subjects claiming disability.

F. X., a young man of twenty-two, (figure 5, section 4), following an empyema operation, had been disabled by pains in the left chest and shortness of breath as soon as he tried to work. There was no X-ray evidence of limitation of motion of the diaphragm, nor appreciable lung disease. Tracings at the right of section 4 show the extreme variability of the patient's performance during quiet breathing, and when directed to take vital capacity (A on spirogram) and maximum breathing determinations (B on spirogram). The best vital capacity tracing was only 1,000 cc. and maximum voluntary breathing about 10 litres per minute. Without the knowledge of the patient, the soda lime container was then removed from the spirometer, and the tracings at the left of section 4 (C) were taken. After a few minutes the patient realized that he was overbreathing and disconnected himself from the apparatus, but the spirograms obtained demonstrate a marked contrast with the voluntary

tracing: a deep regular type of breathing, far exceeding the voluntary hyperventilation in amplitude (2,000 cc.) and in total ventilation per minute (32 litres).

(7) *Respiratory neuroses in organic pulmonary disease:* It is now recognized that, in many patients with definite organic pulmonary disease and pulmonary insufficiency of various types, there may coexist a very considerable factor of respiratory neurosis, aggravating the subjective sensations of dyspnoea, or asthma, and further incapacitating the patient physically. Patients with pulmonary fibrosis of various types, with bronchial asthma and other recurring or chronic diseases may suffer in this way from additional disability on a psychoneurotic basis. The careful study of the patient's form and capacity of breathing will often aid in the analysis of these factors. Space does not permit adequate description of such cases in this paper.

DISCUSSION

The cases which we have described in this paper are illustrative of various clinical conditions in which the spirogram may give valuable and more or less quantitative information. It may be of interest to summarize briefly the significance and usefulness, for clinical diagnosis, of each of the measurements obtained by the spirographic method.

(1) *Form of quiet breathing:* This spirographic tracing will show the depth and rate of quiet breathing, any retardation in inspiratory or expiratory phase, any change in chest position during the course of quiet breathing, and other variations, cyclic or irregular, of quiet respiration. Such spirograms have been found useful in the clinical diagnosis of more advanced types of emphysema, in chest deformities with restricted breathing, in respiratory neuroses and in malingering.

(2) *Form of deep breathing:* This is of particular value in demonstrating retarded breathing, particularly retarded expiration, and will detect early stages of obstructive pulmonary emphysema or bronchial asthma.

(3) *Lung volumes (vital capacity and its subdivisions):* The significance of restriction in amplitude of breathing, which is the function measured by the ordinary vital capacity technique, is well known. The large reserve air obtained on deep expiration taken from resting midposition of the chest, as compared with the smaller reserve air after a deep in-

spiration, is additional evidence for obstructive emphysema. The failure of successive deep respirations to reach the same expiratory position also points to this condition. The effects of bronchodilator drugs may be quantitated by spirographic technique.

(*4*) *Breathing capacity:* This adds to the measurement of amplitude of breathing the dimension of time, as it measures the total volume of pulmonary ventilation that can be provided by the individual breathing at the time. In many instances it is more closely correlated with the individual's physical limitation than the vital capacity measurement itself. The form of breathing during the breathing capacity procedure, particularly the tendency to small amplitude and very rapid rate, is of further significance in the study of breathing in pulmonary emphysema. By the use of involuntary hyperventilation through the stimulus of carbon dioxide, it has been possible to detect the existence of malingering in certain instances.

(*5*) *Oxygen deficit:* By the use of this technique, it is possible to demonstrate the presence of oxygen want in the blood and bodily tissues as a whole. This information is of importance in evaluating various pathological states, both pulmonary and circulatory. This test gives information somewhat similar to that provided by the measurement of oxygen in the arterial blood, but is less sensitive in most cases than this latter determination.

SUMMARY AND CONCLUSIONS

1. A simple technique is described whereby tracings of respiration can be recorded in normal and pathological subjects. The apparatus is a modification of the ordinary Benedict-Roth metabolism apparatus for graphic registration of breathing. The essential changes are: (*a*) a large nine-litre spirometer, (*b*) large tubing and flutter valves, providing little air resistance, (*c*) a two-speed recording drum, rapid and slow.

2. The measurements used for recording respiration are: (*a*) quiet breathing, (*b*) deep (vital capacity) breathing, (*c*) maximum breathing capacity. Bronchodilator drugs may cause marked changes in amplitude and form of tracings.

3. An additional measurement is the oxygen deficit (the *excess oxygen* absorbed when the subject breathes pure oxygen, as compared with room air). This gives an index of oxygen want.

4. The spirographic technique is of special usefulness in the study of obstructive emphysema. It may provide information of value in cer-

tain cases of cardiac disease, and in such conditions as chest deformities, respiratory neuroses and malingering. It frequently gives objective evidence to explain the nature of the patient's dyspnoea. Spirograms also offer a convenient method of following quantitatively over a period of years a patient's pulmonary function.

5. A number of illustrative cases are described.

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ANOMALIES OF THE HUMAN RESPIRATORY SYSTEM[1]

A Proposed Classification[2]

HOVEY JORDAN

The following summary of a proposed classification of anomalies of the human respiratory system is the outgrowth of a survey of the literature which was made in connection with the study of two similar cases of an anomalous lobe of lung tissue not attached to the respiratory system. A considerable variety of titles was found in this survey and the present rather inclusive classification is presented with the idea that such a system, under which morphologically similar cases can be grouped and considered, may be of some value in the several fields which deal with the respiratory system.

It is planned to present a more detailed discussion of this classification, either in whole or in successive parts, later and to include therein references to the various groups as well as descriptions of some of the cases and personal communications to the author.[4] It is realized that it may be desirable to modify this classification in some respects, as determined by its practicability in use and its application to specific cases or groups of cases.[5]

Some of the groups or subgroups in this classification have already been proposed, wholly or in part, by various authors and it is desired to give full credit in any and all such cases. In view, however, of the

[1] From the Department of Anatomy, College of Medicine, University of Vermont, Burlington, Vermont.[2]

[2] Contributions from the Laboratory of Histology and Embryology.

[3] This classification covers anomalies which are primarily of developmental origin, including congenital metaplasias and excluding those which are primarily postpartum in nature. It excludes anomalies of the oral cavity, nose and pharynx, monsters and conjoined twins. It is based upon the morphology of the formed structure regardless of the cause or the source of the tissue. The classification includes a few conditions which are theoretically possible, as well as cases which have actually been reported.

[4] Several communications have already been received, following preliminary presentation of this classification at various meetings. The author will appreciate further data on additional cases, particularly on the rarer conditions, which can be referred to and included in the fuller account.

[5] The author would also appreciate communications discussing the details of the classification itself.

abbreviated nature of the present report, specific references and bibliography will be postponed until the fuller account is presented.

The classification follows:

If the anomaly being described is associated with abnormalities in other parts of the respiratory system, cross classify or name these associated abnormalities under the appropriate heading in this classification. If associated with abnormalities in other structures or organs, that is, diaphragm, pleura, blood vessels, etc., specify the structure or organ, the nature of the abnormality and its relation to the anomaly being described.[6]

I. ANOMALIES OF THE LUNGS AND OF LUNG TISSUE

A statement concerning, or a description of, the histology of the anomaly to be included in groups A to J inclusive. Groups A to F, inclusive, and I each contain the following subgroups which are not repeated for each group in the following presentation: (*1*) Of both lungs; (*2*) Of the right lung; (*3*) Of the left lung.

A. Complete or essential agenesis (necessarily associated with anomalies of bronchi)

B. Supernumerary lobes (likely to be associated with anomalies of bronchi)

C. Supernumerary fissures, without additional true lobes

D. Subnumerary lobes (likely to be associated with anomalies of bronchi)

E. Normal number of lobes; but lobe or lobes atypical

F. Total or essential absence of lobation

G. Anomalous (accessory) lung tissue attached, often pediculated, to some part of the respiratory system (specify relations and attachment)

1. In thoracic cavity:
    a. Anomalous tissue typical
    b. Anomalous tissue atypical
2. In abdominal cavity:
    a. Anomalous tissue typical
    b. Anomalous tissue atypical

[6] The circulatory and lymph-vascular systems are considered as *other systems* in all divisions of this classification.

H. Anomalous (accessory) lung tissue *not* attached to any part of the respiratory system; but
   1. Attached (usually pediculated) to some other structure or organ (specify relations and attachment)
      a. In thoracic cavity, attached to:
         1′. Mediastinum
         2′. Diaphragm
         3′. Other structures
      b. In abdominal cavity, attached to:
         1′. Stomach
         2′. Other structures.
   2. Incorporated in the wall of another organ or structure (specify the organ or structure)
      a. "Cysts" or other anomalies (specify type)
         1′. In oesophageal wall
         2′. In pleura
         3′. In posterior body wall (subcutaneous)
         4′. In other locations

I. Atelectasis

J. Other gross morphological anomalies, exclusive of those listed above
   1. Congenital cystic malformation

K. Atypical histology, exclusive of that listed above
   1. Congenital metaplasia
      a. Hyperplasia
      b. Adenoma
      c. Other tissue anomalies

II. ANOMALIES OF THE TRACHEA AND BRONCHI

A statment concerning, or a description of, the histology of the anomaly to be included in A, 1 to 9, inclusive, and in B, 1 to 8, inclusive.

A. Anomalies of the bronchi and bronchial tree
   1. Agenesis (associated with anomalies of the lung)
   2. Subnumerary (often associated with anomalies of the lung)
   3. Supernumerary (accessory)
      a. Accessory bronchi
         1′. To a normal lobe, or
         2′. To a supernumerary lobe
      b. Accessory bronchi from trachea (independent of the lung itself)
         1′. With anomalous terminal lung tissue (see II B, 3, c)
         2′. Without terminal lung tissue (specify nature of termination)

4. Bronchial cysts, diverticulae and bronchioceles (local, circumscribed outgrowths, evaginations or dilatations of)
   a. Typical bronchial structure
   b. Atypical bronchial structure
5. Enlargement (simulating, or identical with, bronchiectasis)
6. Constriction (simulating, or identical with, stenosis)
7. Fistula
8. Atresia
9. Other anomalies of gross morphology, exclusive of those listed above
10. Atypical histology, exclusive of that involved in 1 to 9, inclusive

B. Anomalies of the trachea
   1. Agenesis (associated with anomalies of the lung)
   2. Abnormal bifurcation or deviation, exclusive of accessory bronchi
   3. Other tracheal evaginations or outgrowths
      a. Simple tubular
      b. Tracheoceles (including aerocele)
      c. Tracheal lungs
      d. Diverticulae and cysts (local evaginations or outgrowths)
   4. Enlargement
   5. Constriction
   6. Fistula
   7. Atresia
   8. Other anomalies of gross morphology, exclusive of those listed above
   9. Atypical histology, exclusive of that involved in 1 to 8, inclusive

III. ANOMALIES OF THE LARYNX AND EPIGLOTTIS

A statement concerning, or a description of, the histology of the anomaly to be included in A, 1 a to f, inclusive; in A, 2 a and in B 1.

A. Anomalies of the larynx
   1. Of the laryngeal wall
      a. Laryngocele, including aerocele
      b. Enlargement
      c. Constriction
      d. Atresia
      e. Congenital webs
      f. Other anomalies of gross morphology, exclusive of those listed above (including fistula)
      g. Atypical histology, exclusive of that involved in a through f

2. Anomalies of the vocal cords
    a. Atypical gross morphology
    b. Atypical histology, exclusive of that involved in a

B. Anomalies of the epiglottis
1. Atypical gross morphology
2. Atypical histology, exclusive of that involved in 1

IV. SITUS INVERSUS

1. Thoracic
2. Complete

THE CUBAN NATIONAL TUBERCULOSIS CASE-FINDING CAMPAIGN[1]

I. Introduction and Results of Tuberculin Tests

JUAN R. MENCIA, MORTON C. KAHN AND EDGAR MAYER

As is the case in most other countries, tuberculosis is a serious public health problem in Cuba. This island republic has a population of about four million. It is estimated by Dr. John J. Castillo, one of Cuba's prominent phthisiologists, that there are about 5,000 annual deaths from this disease and that some 40,000 persons are in the advanced stages.

Attempts to control tuberculosis, however, have been desultory up to very recent times. The first efforts were made in 1912 with the establishment of a private institution known as the Anti-Tuberculosis League. In that year, also, a clinic was founded which was named in honor of Colonel Furbush of the United States Army.

The Esperanza Sanatorium with a capacity of 100 beds was also built in 1912. This institution was originally constructed for the care of patients with minimal lesions. In 1928 accommodations were added for 200 more beds, and also equipment for a new dispensary. However, it was not until 1935 that plans were formulated for an extensive anti-tuberculosis campaign. The Cuban National Council of Tuberculosis (Consejo Nacional de Tuberculosis) was founded in that year with the end in view of inaugurating an island-wide campaign from a central control organization, under government supervision.

Shortly thereafter five modern dispensaries were built and newly equipped for the city of Havana alone, and one each was constructed in the capitol cities of the other five provinces. Esperanza Sanatorium has recently been enlarged so as to accommodate 1,000 patients. This is a thoroughly modern institution.

In the mountains near the city of Trinidad a second sanatorium which will have 1,000 beds is now under construction. As the program reaches fulfilment there will be a centrally located sanatorium for each of the other five provinces.

[1] From the National Tuberculosis Council of Cuba, the Departments of Public Health and Medicine, Cornell University Medical College, New York City.

In January, 1937 the American members of this Committee were invited by Colonel Fulgencio Batista to organize and inaugurate a case-finding campaign. After a series of preliminary conferences the active work was begun in July, 1937.

The first step was to find a suitable district in which to inaugurate the work. The city of Havana was carefully studied and the so-called San Miguel district was selected for this purpose. This district has a population of some 150,000 and is representative of one of the middle and lower class portions of the city. Moreover, there are also to be found in the same locality indigents and very poor people living in so-called yard houses, somewhat similar to those encountered by Opie and his colleagues in Jamaica.

These yard houses present a most interesting epidemiological problem. In Havana, they usually contain some 20 to 30 families. Therefore the term "contact" as regards such localities implies much more than family or household relationship.

Funds are made available to the National Council of Tuberculosis directly from government treasury. Additional support is obtained from the proceeds of the lottery which is also under government supervision. Monies for the Survey under discussion are forthcoming from these sources.

The principal handicap to the program as outlined by the Committee was the great cost of X-raying those who would be found reacting positively to the tuberculin test. The Cuban members of the Committee were urged to study this matter independently, and, accordingly, sent a delegation to New York City in the early spring of 1937. After a thorough investigation of the matter the Powers rapid paper film method was adopted as it appeared that the contemplated service could thereby be extended to a greater number of persons, enabling the staff to take as many films per day as seemed desirable.

During the first part of the Survey the rolls of film were expressed to New York for developing and then reshipped to Cuba. This procedure did not prove satisfactory because of unavoidable delay. Therefore, at the suggestion of the Committee, a complete developing unit has been installed at Esperanza Sanatorium near Havana, which has placed the Survey on an entirely independent basis.

The quality of the radiographs obtained by this method is quite satisfactory. After acquiring a little practice in the reading of the paper films, the radiographers feel confident that they rarely miss anything of

importance. Furthermore, the paper radiograms have been checked with celluloid in a number of instances and satisfactory comparative results were obtained.

As soon as evidence of the disease is discovered, whether clinical or latent, the patient is sent to one of the various institutions which are under the control of the Cuban National Council of Tuberculosis (dispensaries or sanatoria).

The Survey's duties are limited exclusively to case-finding and to epidemiological studies of families where there has been exposure.

The infectivity rate of the Cubans is unknown, nor has there been, up to very recent times, accurate reporting of deaths from tuberculosis. In common with other Latin countries, a death from tuberculosis in a family has been considered a social stigma; therefore, certain family physicians have employed various subterfuges to disguise deaths from this cause. Stringent laws are now being enacted to obviate this difficulty. The National Council of Tuberculosis has an excellent Department of Vital Statistics, including a staff of well trained technicians and modern apparatus. All of the records are reported to this department.

Propaganda: Prior to, and during the Survey, a number of nation-wide radio addresses have been given by both the Cuban and American members of the Committee. The press responded most liberally, publishing numerous editorials, news items and photographs. Thousands of leaflets and handbills were given out in the district under consideration, and a large quantity of posters were pasted on bill-boards, buildings, street-cars and in shop windows. Aside from this legitimate propaganda, absolutely no coercion or intimidation has been used upon the population.

The response has been most enthusiastic and intelligent—the staff of the Survey being employed to its fullest capacity.

The present communication covers the work completed to May 1, 1938. It will be noted that 27,000 tuberculin tests were completed and over 10,000 radiographs. During the months of October and November, the work was almost at a standstill in view of the fact that the building of the permanent Survey headquarters had not yet been completed, and the temporary quarters were inadequate for the task at hand.

The task before us is far from completed, but it seems advisable to bring to the attention of those interested the purposes and accomplishments of the Survey periodically, rather than to await a final report which would be considerably delayed and voluminous.

TUBERCULIN TESTS

The tuberculin selected for this Survey was the Purified Protein Derivative developed by Seibert (1) and her associates. This substance has been recommended as a standard by the Committee on Medical Research of the National Tuberculosis Association.

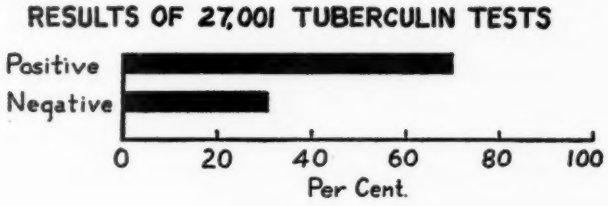

CHART 1

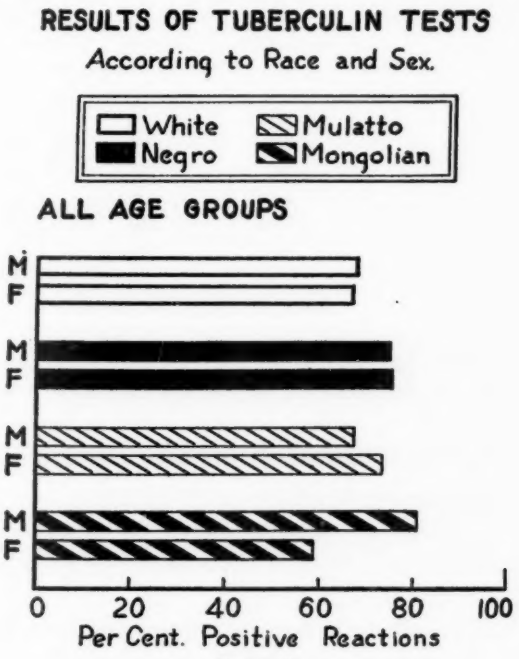

CHART 2

Experience has shown (2) that the problem of deterioration in the tropics is avoided by employing this preparation.

The injections were made on the flexor surface of the forearm in the usual manner. The dosage recommended by the Committee was

scrupulously followed. The first test strength consists of 0.000,02 mg. of PPD. This is claimed to correspond to 1 cc. of Koch's Old Tuberculin in a dilution of 1:25,000 (0.04 mg. OT).

The second test strength consists of 0.005 mg. This second dose was given to all failing to react to the first. We do not apply a stronger dose to children under five who fail to react to the initial injection and only one-half of the second dose is given to those between five and ten years, as a few severe reactions have been obtained.

The first tuberculin test is administered by visiting teams composed of a physician and two nurses. In that way the district is covered in a systematic manner. The reactions are read forty-eight hours later by second teams whose duties are limited strictly to reading and measuring

TABLE 1

Percentage of positive tuberculin tests according to race and sex

	TOTAL TESTS	POSITIVE	NEGATIVE	PER CENT POSITIVE
White males	6,304	4,238	2,066	67.23
White females	9,509	6,367	3,142	66.96
Negro males	2,284	1,693	591	74.12
Negro females	3,341	2,520	821	75.43
Mulatto males	2,062	1,397	665	67.75
Mulatto females	3,310	2,440	870	73.72
Mongolian males	135	109	26	80.74
Mongolian females	56	33	23	58.93

the tests and to applying the second dose to nonreactors. The reactions toward this second injection are also read by the latter teams.

A bus is available to bring the positive reactors to the Survey Headquarters where the X-ray apparatus is installed. Here, too, are a well equipped laboratory and technicians for the purpose of examining sputum by direct smear, culture and guinea pig inoculation, for making blood tests, urine examinations and such other laboratory examinations as are required.

Some 27,000 tuberculin tests were completed and read, and about 3,000 other tests were lost because of the failure of the patient to report back to the clinics or because of the fact that when the testing teams made their visits to the home the persons were out. In this event a card was left requesting them to report to the clinic, but this was not always done.

It will be noted that, of the 27,000 tests completed, 18,797 were posi-

tive (69.62 per cent) and 8,204 were negative. The results in chart 1 are given without regard to age, race or sex.

TABLE 2

Percentage of positive tuberculin tests according to age

	TOTAL TESTS	POSITIVE	NEGATIVE	PER CENT POSITIVE
0 to 1 year	194	31	163	15.98
1 to 4 years	1,319	249	1,070	18.88
5 to 9 years	6,541	3,722	2,819	56.90
10 to 14 years	11,659	8,293	3,366	71.13
15 to 19 years	1,914	1,529	385	79.89
20 to 34 years	2,929	2,682	247	91.57
35 to 59 years	2,071	1,941	130	93.72
60 years and over	374	350	24	93.58

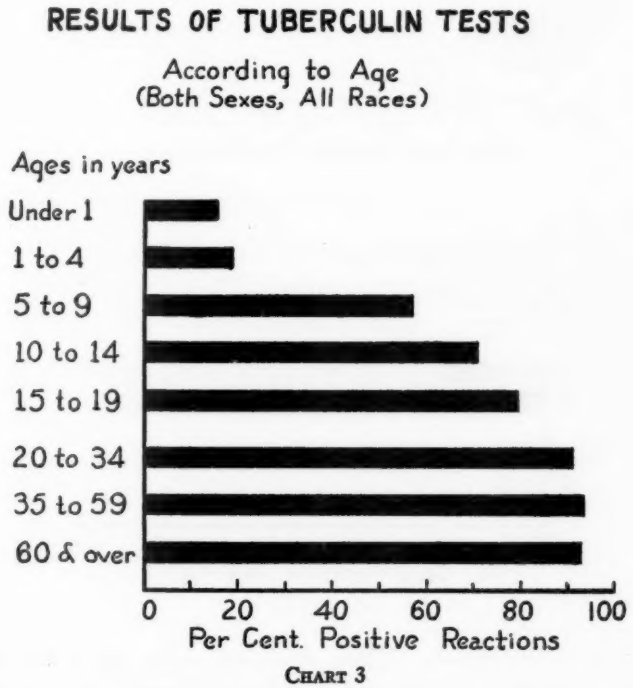

CHART 3

Table 1 and chart 2 indicate the results obtained according to race and sex. It seems that the whites, Negroes and Mulattos do not vary considerably as regards the percentage of positive reactors, but the Negroes

do reveal a somewhat higher rate. Chinese males revealed the highest percentage of reactors while the Chinese females, interestingly enough, revealed the lowest rate. The Chinese males in Havana are usually employed in the restaurant or laundry business or are engaged in market gardening. In most cases they conscientiously pursue their tasks in

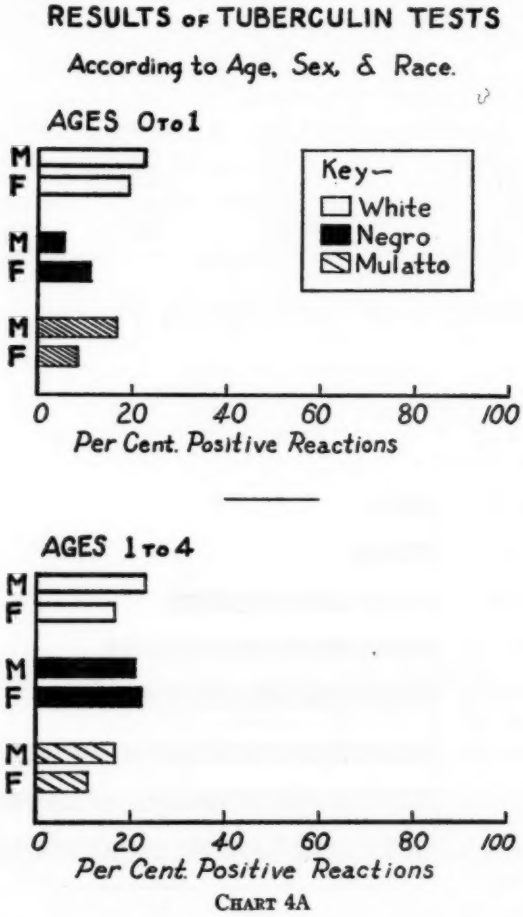

CHART 4A

order to gain a livelihood. Their working hours are long, and their housing and diet often inadequate. Chinese women do not engage in industry, their duties being limited strictly to those of the household.

Table 2 and chart 3 show the results of the tuberculin tests analyzed according to age without regard to sex or race. When the second decade is reached, 91 per cent and over are positive.

Charts 4A, B, C and D, with their accompanying table 3, analyze the positive reactors according to age, sex and race. In the age groups under one year, those of the white race reveal a larger percentage of positives than either the Negroes or Mulattos. After that time, however, it will be seen that the Negroes show a slightly greater number of positives, but

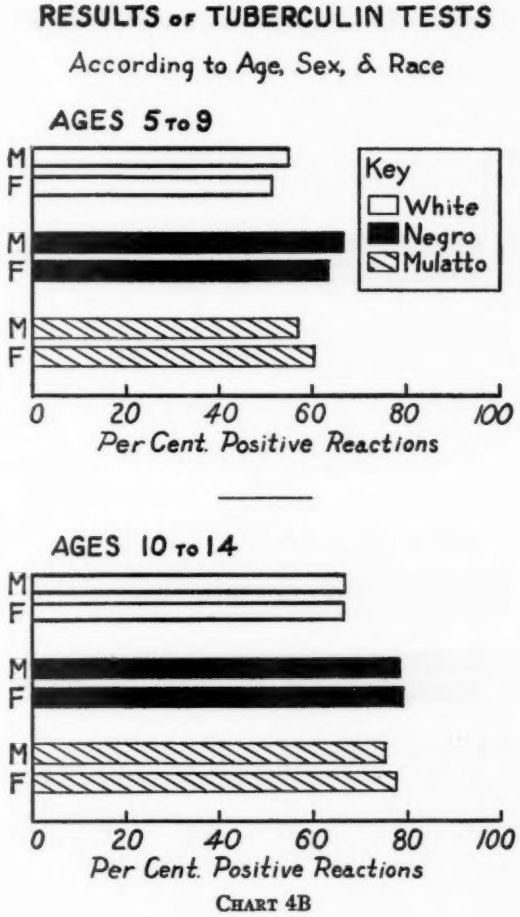

CHART 4B

the difference is so little that we hesitate to attach any significance to this observation.

These results would indicate that whites, Negroes and Mulattos, living under comparable economic conditions in the tropics, become infected at almost the same rate.

The results summarized in chart 5 and tables 4 and 5 are most interesting. It will be noted that over 30 per cent gave a 1+ reaction on the initial injection of PPD. Almost 9 per cent revealed a 2+ reaction. Those having the 3+ amounted to 3.58 per cent, while those giving the 4+ reaction amounted to 1.2 per cent of the 27,000 tested. The usual

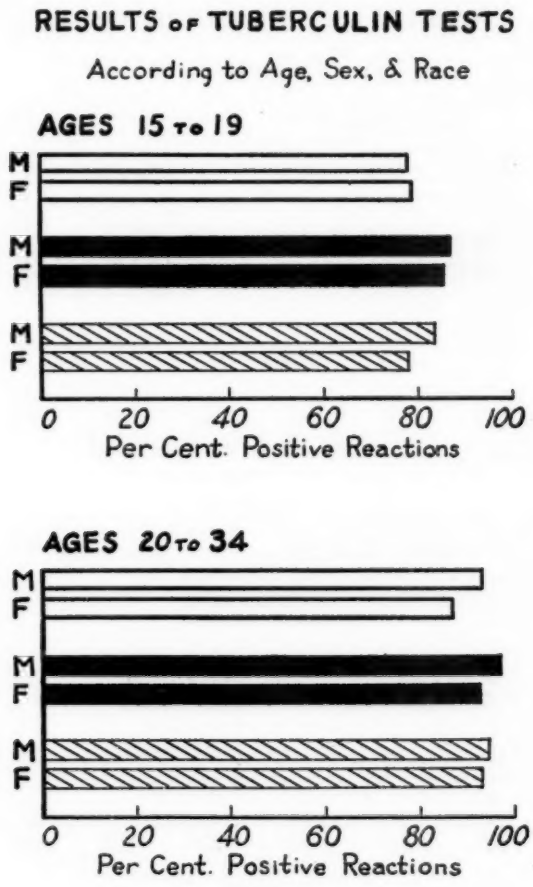

CHART 4C

criteria of reading and measuring these tests were employed. In comparison, relatively few required a stronger injection of PPD, but it may be noted from table 5 that 10.44 per cent gave rise to a 1+ reaction, 5.29 per cent revealed a 2+ reaction, 2.1 per cent were 3+, while only 1 per cent revealed the 4+ reaction.

As Myers (3) states, no doubt tuberculin tests have been greatly over-read. Doubtless small areas of hyperaemia with no oedema have been considered as positive reactions, when, in reality, they are of no significance. Myers feels that for practical purposes it is not necessary to read the degree of reaction, since this, apparently, is of no significance so far

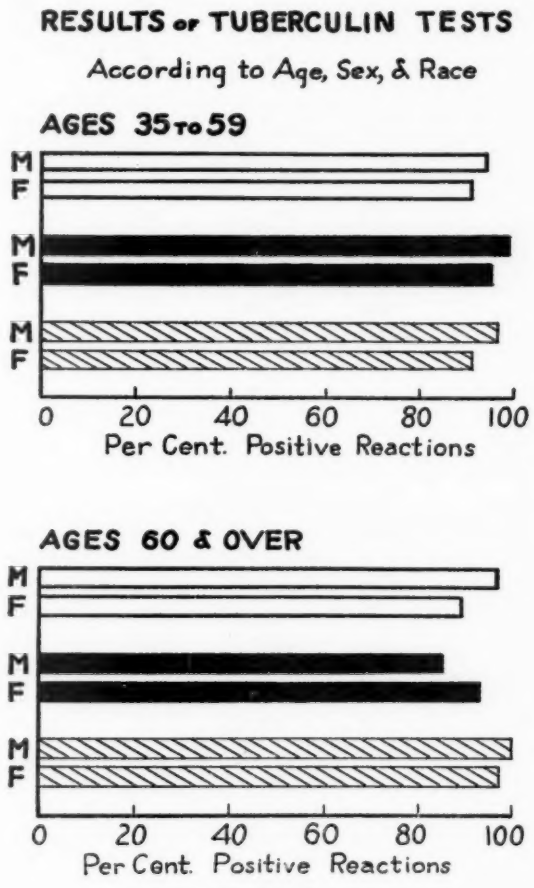

CHART 4D

as the extent of the disease is concerned. This may or may not be the case, but, in view of the fact that the infectivity rate of the Cubans has been unknown, we thought it best to gather as many data concerning the reactions as possible. We reported no tests as positive unless an area of induration was present.

TABLE 3

Results of tuberculin tests according to age, sex and race

	TOTAL TESTS	POSITIVE	NEGATIVE	PER CENT POSITIVE
Ages 0 to 1				
White males	53	12	41	22.64
White females	41	8	33	19.51
Negro males	18	1	17	5.56
Negro females	27	3	24	11.11
Mulatto males	30	5	25	16.67
Mulatto females	24	2	22	8.33
Mongolian males	1	0	1	0.00
	194	31	163	15.98
Ages 1 to 4				
White males	283	64	219	22.62
White females	294	48	246	16.33
Negro males	174	38	136	21.84
Negro females	208	47	161	22.60
Mulatto males	163	29	134	17.79
Mulatto females	193	22	171	11.40
Mongolian males	3	1	2	33.33
Mongolian females	1	0	1	0.00
	1,319	249	1,070	18.88
Ages 5 to 9				
White males	1,529	831	698	54.35
White females	2,236	1,190	1,046	53.22
Negro males	624	413	211	66.19
Negro females	788	501	287	63.58
Mulatto males	625	355	270	56.80
Mulatto females	674	406	268	60.24
Mongolian males	35	14	21	40.00
Mongolian females	30	12	18	40.00
	6,541	3,722	2,819	56.90
Ages 10 to 14				
White males	2,917	1,964	953	67.33
White females	4,460	3,001	1,459	67.29
Negro males	908	710	198	78.19
Negro females	1,270	1,001	269	78.82
Mulatto males	807	606	201	75.09
Mulatto females	1,284	1,001	283	77.96
Mongolian males	3	3	0	100.00
Mongolian females	10	7	3	70.00
	11,659	8,293	3,366	71.13

TABLE 3—*Concluded*

	TOTAL TESTS	POSITIVE	NEGATIVE	PER CENT POSITIVE
Ages 15 to 19				
White males	395	307	88	77.72
White females	737	577	160	78.29
Negro males	108	93	15	86.11
Negro females	246	211	35	85.77
Mulatto males	122	102	20	83.61
Mulatto females	300	234	66	78.00
Mongolian males	5	4	1	80.00
Mongolian females	1	1	0	100.00
	1,914	1,529	385	79.89
Ages 20 to 34				
White males	652	611	41	93.71
White females	988	860	128	87.04
Negro males	210	202	8	96.19
Negro females	402	375	27	93.28
Mulatto males	190	179	11	94.21
Mulatto females	453	422	31	93.16
Mongolian males	21	21	0	100.00
Mongolian females	13	12	1	92.31
	2,929	2,682	247	91.57
Ages 35 to 59				
White males	365	343	22	93.97
White females	626	569	57	90.89
Negro males	221	218	3	98.64
Negro females	355	340	15	95.77
Mulatto males	103	99	4	96.12
Mulatto females	337	309	28	91.69
Mongolian males	64	63	1	98.44
	2,071	1,941	130	93.72
Ages 60 and over				
White males	110	106	4	96.36
White females	127	114	13	89.76
Negro males	21	18	3	85.71
Negro females	45	42	3	93.33
Mulatto males	22	22	0	100.00
Mulatto females	45	44	1	97.78
Mongolian males	3	3	0	100.00
Mongolian females	1	1	0	100.00
	374	350	24	93.58

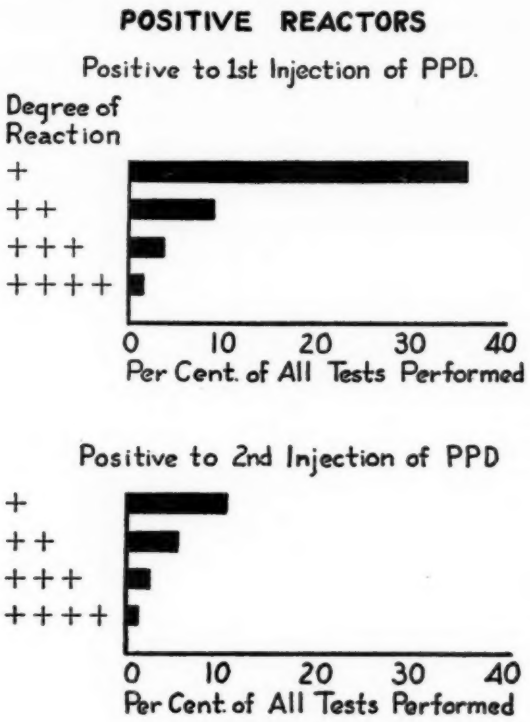

CHART 5

TABLE 4

Degree and per cent of positive reactors to 1st injection of PPD compared to total tests performed

THOSE WITH	PER CENT
+	30.58
++	8.94
+++	3.58
++++	1.22

TABLE 5

Degree and per cent of positive reactors to 2nd injection of PPD compared to total tests performed

THOSE WITH	PER CENT
+	10.44
++	5.29
+++	2.10
++++	1.00

It gives us great pleasure to acknowledge the coöperation of Colonel Fulgencio Batista, Lt. Colonel Dimitrio Despaigne, President, Consejo Nacional de Tuberculosis, Dr. Wilson G. Smillie, Professor of Public Health and Preventive Medicine, Cornell University Medical College, and Dr. John C. Torrey, Professor of Epidemiology, Cornell University Medical College.

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THE CUBAN NATIONAL TUBERCULOSIS CASE-FINDING CAMPAIGN[1]

II. Results of X-ray Studies

JUAN R. MENCIA, EDGAR MAYER AND MORTON C. KAHN

The morbidity rate of tuberculosis is still not determined and knowledge of the incidence of open tuberculosis is likewise inadequate. In the United States the general death rate from tuberculosis is rather accurately defined from mortality statistics. However, in Cuba figures so far are most incomplete. The frequency of clinically manifest lesions, latent tuberculosis and residual lesions has not, up to now, been determined in the Island of Cuba. Therefore studies such as the present are essential in an attempt to eradicate the disease from the Island.

Early diagnosis has long been one of the most discussed chapters of tuberculosis. This was undoubtedly so because knowledge of it has always been rather vague. It is not an overstatement that the beginning of chronic pulmonary tuberculosis presents still many problems. Particularly has this been shown in the last few years by intensified case-finding campaigns and large scale X-ray surveys, which have proved to be enormously efficient in detecting early disease. These surveys have, however, greatly accentuated our problem of diagnosis and proper selection of cases for treatment.

Judging from the figures of recent American X-ray surveys, 3 to 5 per cent of possibly clinically significant tuberculous lesions were found in the population as a whole. Slightly less than 1 per cent have clinically manifest tuberculosis and are known to be ill. Radiographs show approximately 1 per cent who, though presumably well, have tuberculous lesions in the pulmonary apices so advanced as to extend below the clavicle. A somewhat larger number of adolescents and young adults have minor but potentially significant apical lesions. Among adolescents in school between the ages of fifteen and nineteen, about 1.5 per cent have tuberculous lesions of the lung so advanced as to be recognized by X-ray, the potential significance of which is greater in the girl. About

[1] From the National Tuberculosis Council of Cuba, the Departments of Medicine and Public Health, Cornell University Medical College, New York City.

one of every six white adults dying from diseases other than tuberculosis shows by autopsy partially caseous lesions at one of either apex of the lung; in about two-thirds of these, virulent tubercle bacilli may be found (Opie). In the United States the problem still exists of diagnosis and management of tuberculosis in a few million people.

The enormous economic and public health tasks which the turn of events implies are obvious. Our entire antituberculosis program will have to be reoriented in accordance with the ultimate solution of these questions. We must accordingly establish definite standards of early diagnosis.

It is not sufficient now merely to diagnose active pulmonary tuberculosis in its earliest phase. The problem is one of discriminating first between the manifestly *active* and the *latent* pulmonary lesion, that is, one with the potentiality of progression, and second of discriminating between the latter and a definitely *obsolete* lesion.

Modern X-ray surveys have revealed large numbers of apparently healthy individuals harboring in their lungs demonstrable lesions of tuberculosis. In the great majority of these persons the lesions represent the residues of old tuberculous infections which are healed. In a certain proportion of these the lesions undoubtedly represent a latent process with potentiality for progression. It has been further shown that the yearly crop of patients with chronic pulmonary phthisis is not developed exclusively from the people harboring the lesions which were previously demonstrated by X-ray. What proportion of our chronic pulmonary tuberculosis represents the progression of latent lesions previously demonstrated by X-ray survey and what proportion comes from sudden unexpectedly developed lesions is yet far from understood. What criteria will determine the type of latent X-ray lesion likely to progress and the type of lesions likely to appear unexpectedly in a chest previously normal is still undecided. It is upon such information that our standards for the diagnosis of early pulmonary tuberculosis will have to be established.

Until accumulated experience ultimately affords a definite answer to all these questions our diagnostic work continues to be based on studies such as the present. The three divisions of residual, latent and manifest tuberculosis are eminently suited for classification and have been used by us in this case-finding campaign conducted for the past two and one-half years in the Island of Cuba.

Residual images are those of calcified nodules in the lungs of single or multiple primary complexes, with associated tuberculous tracheo-

bronchial or mediastinal calcified lymph nodes. Also included are fibrotic scars and pleurodiaphragmatic adhesions, such as tenting of diaphragm or obliterated costophrenic sulci.

Latent tuberculosis includes potentially progressive shadows such as latent infiltration of first infection or childhood infiltration of soft, flocculent, strand-like nature, latent apical reinfection or adult-type tuberculosis which may take the form of supraclavicular apical salients or spots to below the second rib posteriorly, not exceeding in extent minimal or moderately advanced tuberculosis.

Clinically manifest tuberculosis comprises a group in which there is massive caseous tuberculous tracheobronchial lymph nodes and adult-type reinfection tuberculosis with or without tubercle bacilli in the sputum.

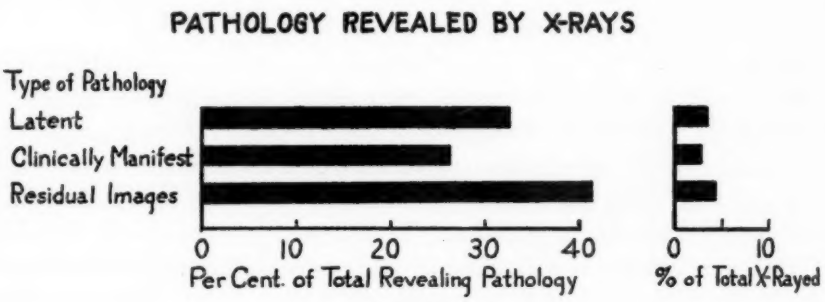

CHART 1

Results of X-ray examinations: The total number of radiographs taken in this series was 10,949 of which number 1,136, or 10.38 per cent, revealed lesions. According to the type of lesions seen, 470, or 41.38 per cent, were *residual images*. This number represents 4.29 per cent of the total number of persons X-rayed in the Survey.

Latent tuberculosis was seen in 369, or 32.48 per cent of pathological films, and represents 3.37 per cent of the total number of persons X-rayed.

Clinically manifest lesions were demonstrable in 297, or 26.14 per cent of pathological radiographs or 2.71 per cent of the total number X-rayed. (Chart 1.)

INCIDENCE OF ALL FORMS OF LESIONS AS TO AGE GROUPS

When radiographs revealing lesions were considered according to age groups of greatest disease incidence, it was found that 50 per cent of the

total cases showing disease were in ages twenty to thirty-four and thirty-five to sixty, and another 25 per cent in the group ten to fourteen years (chart 2). Thirteen and one-third per cent were in the five to nine group and 7.83 per cent in the fifteen to nineteen years age group. There was very little difference between sexes, females presenting a slightly greater percentage than males. Thus it will be seen that tuberculosis has its greatest incidence of morbidity in the age groups of youth, in the period of puberty, and in man's economic and biological prime.

Residual images: (Charts 3A and 3B.) When residual images alone were considered according to age they were found to be of greatest in-

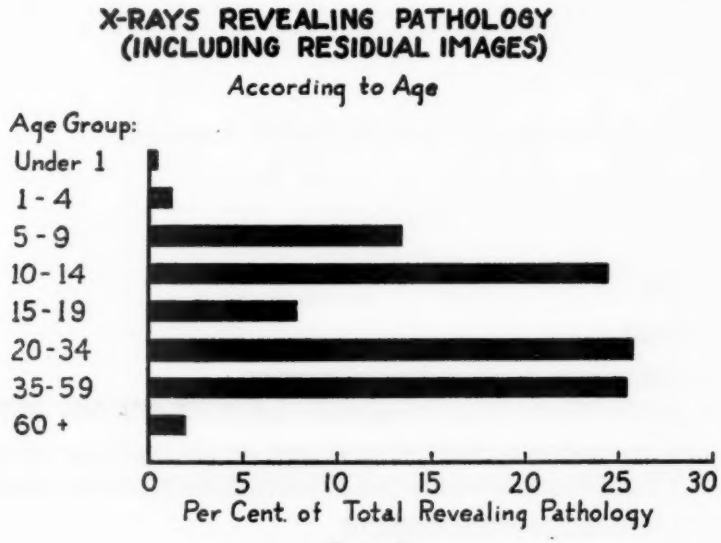

CHART 2

cidence in the group from ten to fourteen years, in which they were found in 183, or 16.11 per cent of the total number revealing lesions or 1.67 per cent of all persons studied in the Survey. About half this number (94) were found in children from five to nine years. Next in frequency was the age group of twenty to thirty-four years, 86, or 7.57 per cent of the total, revealing lesions. Females revealed a slightly greater number of residual images than males.

It is apparent from a study of the foregoing charts that residual images reach their greatest incidence during puberty and the preadolescent period while latent and clinically manifest tuberculous disease is of

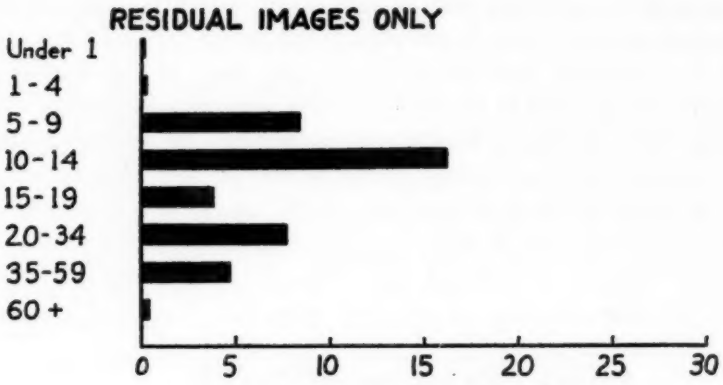

CHART 3A

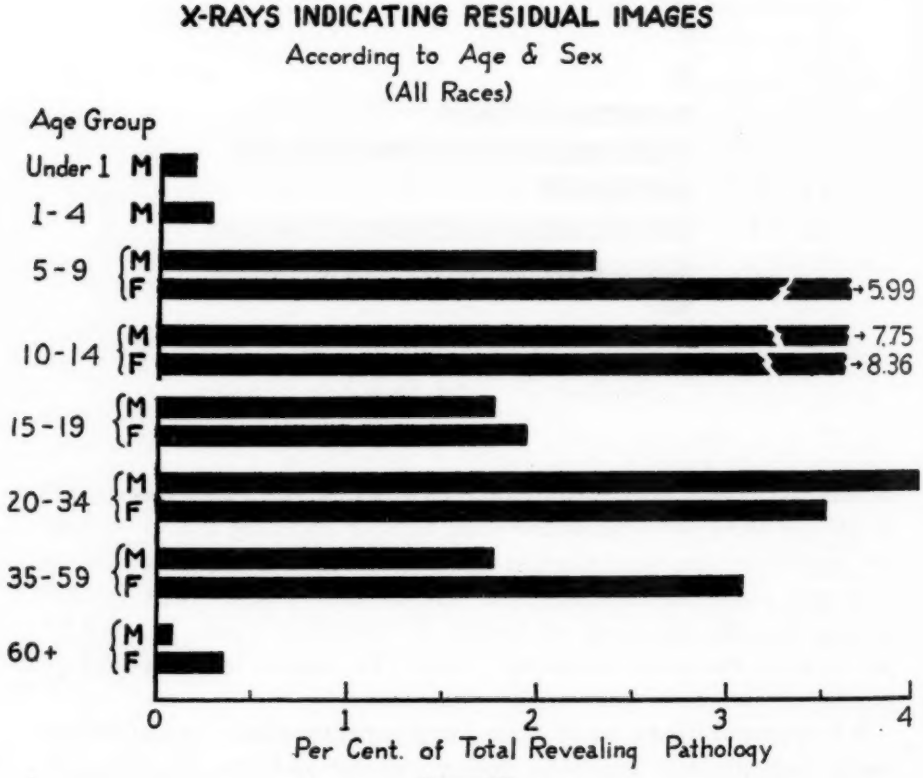

CHART 3B

greatest incidence in young adult years and ages twenty to thirty-four and thirty-five to sixty.

Latent tuberculosis as to race and age groups in Cubans of white, Mulatto and Negro races: (Charts 4A and 4B.) The greatest incidence is in the age groups five to fifteen and twenty to sixty. The incidence of latent

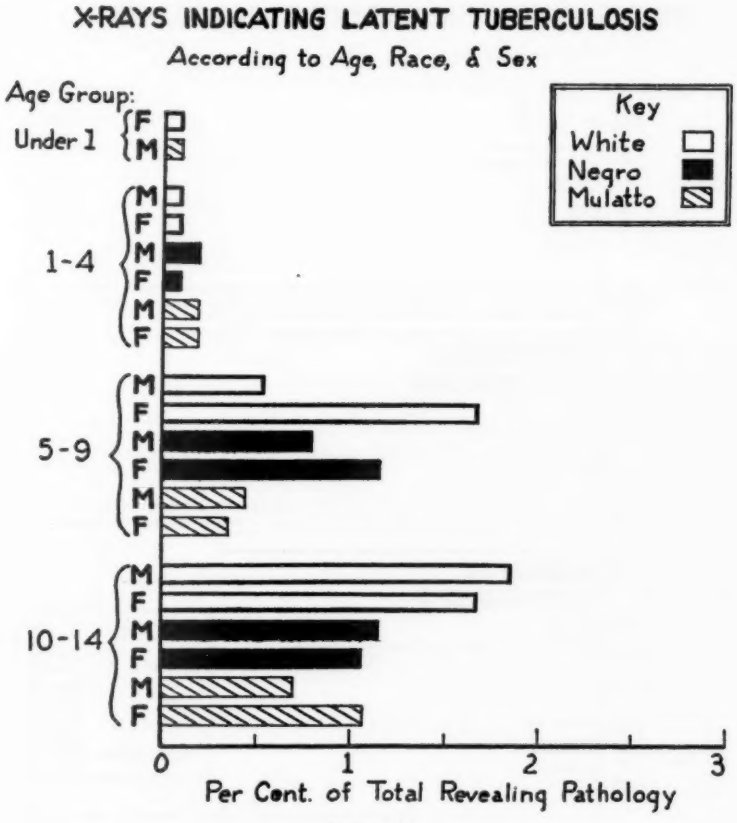

CHART 4A

tuberculosis in the whites far exceeded that found in Mulattos and Negroes in these periods. In white persons from twenty to sixty the incidence of latent tuberculosis was more than double that of Mulattos and Negroes of the same age period. Females had slightly greater incidence than males.

Clinically manifest tuberculosis reaches its peak of incidence in ages

from twenty to sixty, particularly in ages thirty-five to fifty-nine (charts 5A and 5B). In whites the curve of the frequency of manifest lesions ascends from age fifteen to sixty. Whites far exceed Mulattos and Negroes during these ages. Mulattos have a greater number of manifest lesions than do Negroes in this Survey.

CHART 4B

Occupation: In chart 6 are summarized all persons X-rayed according to occupation (in occupations in which more than 50 were studied). The highest incidence of tuberculosis occurred in unemployed and in chauffeurs; least in college students and professional men. Housewives, journalists and laborers were intermediate in case incidence.

X-RAYS INDICATING CLINICALLY MANIFEST TUBERCULOSIS

According to Age, Race, & Sex

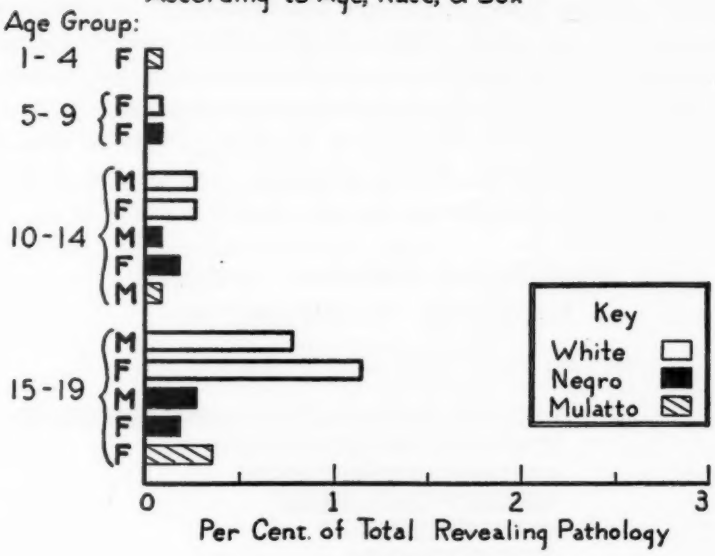

CHART 5A

X-RAYS INDICATING CLINICALLY MANIFEST TUBERCULOSIS

According to Age, Race, & Sex

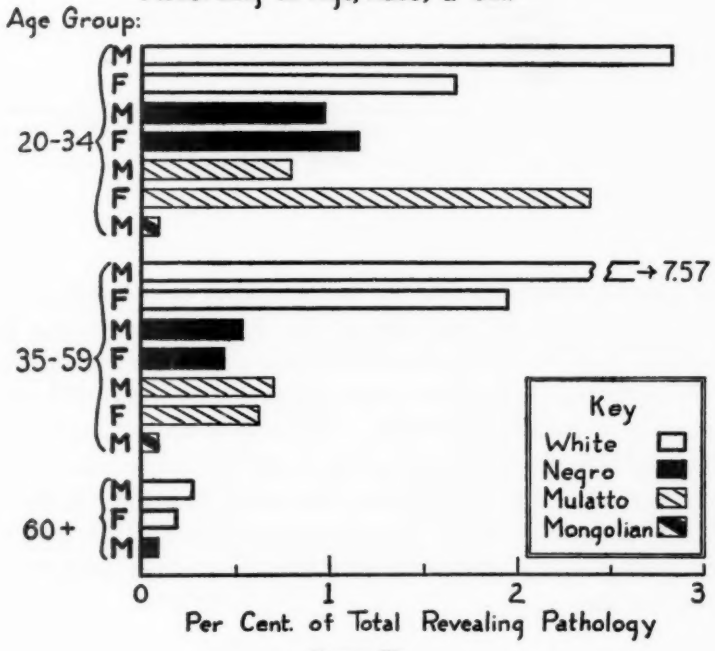

CHART 5B

Of 10,949 persons X-rayed, 1,136, or 10.38 per cent, revealed pathological changes. Of this number 470, or 41.38 per cent, consisted of residual X-ray images, 369, or 32.48 per cent, presented latent tuberculosis and 297, or 26.14 per cent, presented clinically manifest lesions.

Thus, of the total number X-rayed in the Survey, 4.29 per cent showed images of residual, 3.37 per cent of latent and 2.71 per cent of clinically manifest tuberculous disease.

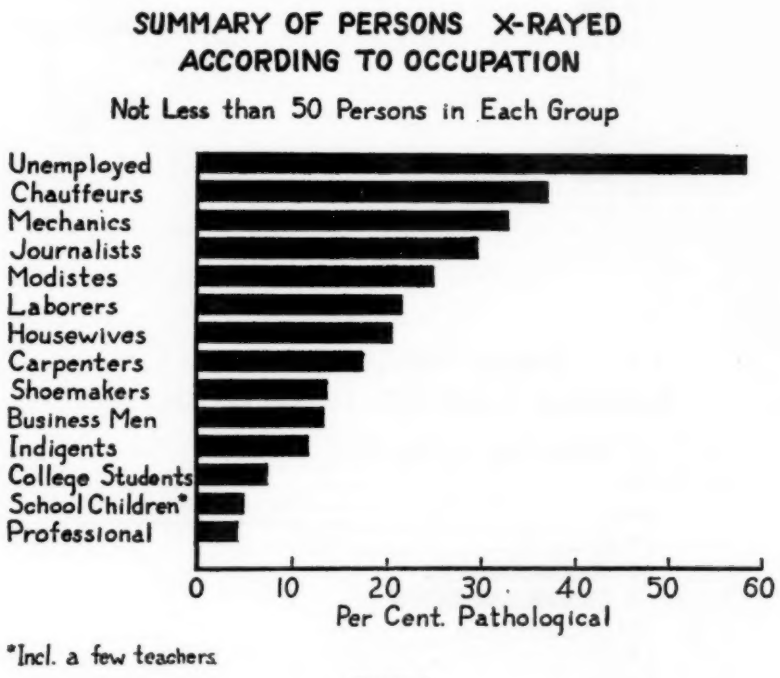

CHART 6

Considering the incidence of the various types of pathological lesions according to radiographs from among the persons in this series by age, sex and race, it was found that residual images were of greatest incidence in the age group ten to fourteen years, occurring in 16.11 per cent of the total number of pathological films. There were half as many residual images in children of five to nine years of age (94 cases). In the twenty to thirty-four years age group there were residual images in 86, or 7.57 per cent of the total number of pathological films. This type of pulmonary change was encountered with slightly greater frequency in females than males.

Considering all forms of pulmonary tuberculous lesions, 50 per cent were in ages twenty to thirty-four, 25 per cent in ten- to fourteen-year group, 13.3 per cent in five- to nine-year group and 7.83 per cent in fifteen- to nineteen-year group. Females presented a slightly greater incidence of pulmonary disease.

Residual images were of greatest incidence during puberty, while latent and clinically manifest tuberculosis occurred more frequently in young adults and ages thirty-five to sixty.

Considering the factor of race in the incidence of tuberculosis in the whites, Mulattos and Negroes of Cuba, it was found that latent tuberculosis in whites far exceeded that found in Mulattos and Negroes in the age groups five to fifteen and twenty to sixty and was more than double that in Mulattos and Negroes in the twenty- to sixty-year group.

Whites, in this Survey, were found to exceed by far the Mulattos and Negroes having clinically manifest disease in ages twenty to sixty, especially thirty-five to fifty-nine. Mulattos presented a greater number of manifest lesions than were seen in Negroes.

The highest incidence of tuberculous lesions were in unemployed persons and chauffeurs, probably due to poor standard of living conditions, lack of sufficient food, low pay and irregular hours of work. College students and professional men had the smallest incidence of disease.

THE EVOLUTION OF MODERN PNEUMOTHORAX MACHINES

II. Fluid-free Apparatus and Continuous Reversal Apparatus

LOUIS R. DAVIDSON[1]

We have grouped together modern pneumothorax apparatuses into four types—hydrostatic, bellows, fluid-free and continuous reversal. The former two have already been described in the previous paper. We shall now proceed to the latter two.

FLUID-FREE APPARATUS

The apparatuses described in this group are usually very simple devices consisting mainly of balloon and tubing, syringe and plunger, cylinder and piston or similar components which make for compactness and portability.

Forlanini (119), even in his days, recommended for refills in the home a very simple combination of rubber bulb (300 cc. capacity) and tubing with filter and needle. The bulb is filled with nitrogen and is carried to the bedside. One stopcock, situated along the tubing, opens and closes the instrument.

Benedetti (120), in 1918, described a similar arrangement using a Champetier de Ribes balloon. He claimed that, in addition to being very simple, this was a safe all-round instrument, for the touch of the human hand is as sensitive a manometer as any.[2]

Challonel (121), in 1919, recommended a simple sphygmomanometer bulb of known capacity to insufflate air into the chest. Bond (122), in 1928, used a similar apparatus.

Severini (123), in 1925, interposed in the delivery tube a copper coil which he heated by means of an alcohol flame.[3] In addition to the usual

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[2] Benedetti even went the length of stating that the common accidents of pneumothorax can be avoided with this instrument.

[3] The author felt that the insufflation of cold air is the most probable cause of pleurogenic shock and therefore used air heated to body temperature.

water manometer, he employs a sensitive diaphragm that oscillates synchronously with the respiratory excursions.

Morelli (124), in 1917, described a modification of Forlanini's simple bulb. To prevent the insufflation of gas at more than atmospheric pressure, he added a collapsible balloon which serves as a gas reservoir (figure 7). A Richardson bulb is used to fill this balloon and, when communication of the latter is established with the pleural space via the delivery tube and needle, the nitrogen used is sucked in by the negative intrapleural pressure and is not expressed.

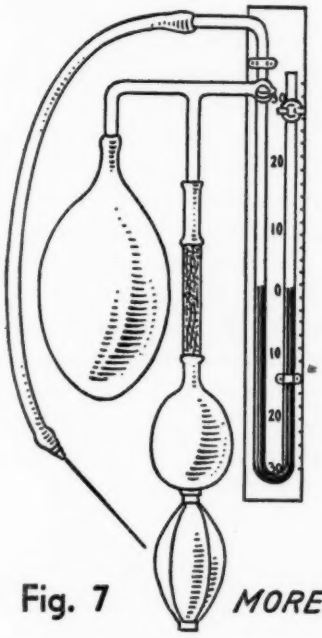


Fig. 7 MORELLI

Marshall (125), in England, four years later, offered a modification of Morelli's unit, using a 400 cc. india-rubber bag as gas reservoir fitted with a three-way valve, so that air, nitrogen or carbon dioxide can be admitted.

Pongs (126), in 1920, used an ordinary record syringe of 100 cc. capacity, fitted with a two-way adaptor. On the upstroke, air is drawn through a filter to fill the syringe; on the downstroke, after closing the inlet by turning the cock, air is driven into the chest.

Leschke (127), in the same year, used a cylinder with three outlets, one to the delivery tube, a second to the manometer and a third to a

simple syringe-type pump. A two-way stopcock permits the filling of the pump with air and its expulsion into the cylinder. He later modified his apparatus (128) by making it more stable and by substituting a 150 cc. syringe for the pump. Leschke (129) improved his instrument still further in 1929, by making it as compact as a modern mercury sphygmomanometer. Some four years later, he described his latest modification (130) wherein he employed a 300 cc. syringe and conveniently housed it in a sphygmomanometer case.

Sorgo (131), in 1920, used a small metal syringe of only 1.5 cc. capacity. One hundred strokes are equivalent to 150 cc.

Di Martini (132), in 1924, used a 50 cc. syringe and a two-way adaptor. He provided for the manometer to be kept either continuously in circuit or cut out at will.

Baillet (133) used a vertical cylinder with a heavy piston which plunges of its own weight, displacing the contained air into the cavity.

Jousset (134), in 1922, likewise used a large Luer syringe leading to a T-tube with stopcock, the arms of the T leading to a manometer and to a delivery tube. For use in the home he recommended that any piece of glass tubing dipped into a jug of wine or similar liquid might well serve as an improvised manometer. A special valve is incorporated in the tubing leading to the manometer and it serves to dampen the free oscillations whenever a true measurement of intrapleural pressure is desired.

Lloyd (135), at a later date, modified Jousset's instrument. He attached a reservoir balloon to a simple syringe-type pump and a three-way adaptor and thereby obtained an instrument which allows air to be sucked rather than forced in during primary inductions.

Kohler (136), in 1925, produced two fluid-free models, one for office use, the other for domicile use, employing a metal syringe. During initial inductions a long rubber tubing of 300 cc. is attached to the delivery tube and this serves as an air reservoir from which air is sucked and not pumped into the pleural space.

Di Martini and Wynn (137), in 1926, described a pocket-sized apparatus, enclosed in a carrying case, but this too consists essentially of a syringe that fits into a round glass chamber from which connections lead to manometer and delivery tube.

Heaf (138), in the same year, used a collapsible cylinder, fashioned in the manner of a Chinese lantern. At the bottom lies a special adjustable pressure valve to which is attached the delivery tube to the

needle and to the manometer. At the top lies the inlet tube which is molded in the shape of a handle. The cylinder is unfolded and filled by pulling the handle upward, and is supported vertically by three pillars on which it slides freely. The valve is adjusted to deliver a constant pressure and the cylinder is made to collapse and expel the air through the valve by placing a weight over the top. The author claims that this offers an advantage over the hydrostatic types, because in the latter the pressure varies as the fluid levels change, whereas in his apparatus gas is delivered at constant pressure.[4]

An early model used by Wingfield (139) features a brass hand-pump which expels 50 cc. of air with each stroke. An instrument described in 1927 replaces the pump with a cylinder and piston lubricated with castor oil to insure air tightness and to permit a smooth and regular descent of the piston by its own weight. Other features are a screw valve to regulate the flow of air and a two-manometer system. The manometer nearest to the chest is a simple water manometer and serves chiefly as an oscillometer. The second, an oil manometer,[5] is set at the patient's mean intrapleural pressure and will remain at that level if the displaced air is not introduced too rapidly.

Rossi (140) used a simple syringe as his apparatus.

The Bethune (141) instrument can be used for pneumothorax and for aspiration alternately or simultaneously, if a vacuum bottle is connected in parallel with the delivery tube. It consists of an aluminum cylinder and plunger which is operated by a crank on a worm-gear principle. Starting with the piston at the top and opening the appropriate valve, pneumothorax is obtained. Starting with the piston at the bottom and shutting off the first valve and opening a second, deflation may be obtained. For the simultaneous replacement of pleural effusion with air, the vacuum bottle is first deflated to create suction and then it is connected with a needle introduced into the pleural cavity. A second needle is introduced above the first and is connected with the pneumothorax machine. As fluid is withdrawn the piston is lowered, sending air into the chest.

[4] We feel that this claim is an attribute of the valve only and in that event a similar valve would confer the same advantage to any type of apparatus, hydrostatic or bellows.

[5] A mixture of oil and chloroform is used in such proportion as to give a specific gravity of 1000.

Habliston (142) recommended his compact apparatus which is conveniently housed in a sphygmomanometer box. It consists of a simple double rubber bulb which displaces approximately 50 cc. with each compression.

Gordon (143), in 1931, described an instrument embodying some new features. He uses a metal pump and a copper air chamber, fitted with a pressure gauge, to indicate the volume of air used. Instead of a manometer, he employs a graphic recording device which marks the positive and negative excursions corresponding to the variations of intrapleural pressure.

Wong and Van Allan (144) use a different type of pump which is manoeuvered by a wheel, shaft and bearing. An automatic counter keeps tab of the number of strokes utilized. Turning the wheel clockwise gives inflation, and counter-clockwise, deflation. The manometer is equipped to catch and reutilize the fluid that spills over, while a movable scale facilitates the slight adjustments often necessary to bring the zero mark and the fluid volume to the same level.

Giordano (145), in 1932, and Buera (146), in 1938, recommended instruments consisting of simple syringes with the common adaptors and fittings.

Duboczy (147, 148) used a 700 cc. cylinder and piston which is driven by its own weight. Two years later he offered a modified cylinder and piston so that on the downstroke air is sucked into the cylinder from above and therefore no inlet valve has to be manipulated. The plunger is then rotated 180 degrees and brought back to its original position without discharging the air previously sucked in. Unlike his first model, the cylinder is not fixed in the vertical position and can be tilted toward the horizontal to lower the pressure of the displaced air. During initial procedures, to permit air to be sucked and not forced, the instrument is kept in the horizontal position.

Cutler (71), in 1933, produced a modification of the Loving apparatus. It consists of an air chamber and a pump. The volumes of air used are read directly on a mercury gauge. The chamber is first filled with air by means of the pump and then, by opening a control valve, the air is allowed into the chest and the manometer.

Bottari (149), by adding a number of stopcocks and fittings, utilizes the plain syringe for all the common needs of chest work, including pleural lavage. A rubber balloon, attached to the apparatus, serves as an air reservoir.

Stockwell's (150) instrument features a 100 cc. syringe, a wash bottle and a tambour which serves as manometer. The inner tube is connected to the wash bottle which contains carbolic acid solution. The Jaquet tambour used remains in communication with the delivery tube at all times. It is standardized by calibrating it with a plain water manometer.

Maxwell (151), in 1934, described an apparatus featuring a metal pump consisting of a cylinder fitted with a hollow piston rod. At the top there is a two-way stopcock, shaped in the form of a handle. A clockwise turn of the handle opens the inlet, and the cylinder is filled on the upstroke; a counter-clockwise turn opens the outlet and closes the inlet, while the piston makes a downstroke by virtue of its own weight. A pressure control valve and a manometer complete the instrument.

Minnis (152), in the same year, described a somewhat similar apparatus with a cylinder of 700 cc. capacity, and a piston fitted with leather rings. Weights may be placed on a handle fitted to the piston rod, and the action of the piston is balanced by a system of pulleys and counterweights. By varying the weights, any desired pressures may be obtained. During initial induction no weights are used, so that the gas is not forced into the chest.

Preve (153) described an accordion-like bellows model. A special valve is used to set the apparatus for inflation or deflation. The volumes of air used are read directly from an indicator attached.

Mantoux (154), Behrend (155), Strauss and Kojac (156), Scoyoc (157), Petit (158), Sorgo and Sattler (159) and Hirsch (160) described instruments of the simple syringe type which do not present features differing appreciably from models already described. Petit's carries a device for permitting various inclinations of the barrel, while Sorgo and Sattler's has a table clamp for fixing the instrument wherever it stands. The syringe used by Strauss and Kojac is fitted with X-acto bivalve adaptor, each leg of which is joined with glass valves, moving in opposite directions, so that when the inlet valve is opened the outlet is closed and vice versa. The movements are controlled by the action of the piston. Hirsch's model is furnished with an automatic two-way valve and a sensitive aneroid manometer.

Sciacca (161), in 1936, adopted a special pressure-reducing valve to an ordinary commercial gas tank and made a small, all-metal, unbreakable, portable instrument. The valve is capable of giving any desired pressure, and a meter registers the contents of the gas tank in litres as well as the volume of gas used in cubic centimetres. The manometer is of the aneroid type, connected in parallel with the delivery tube.

CONTINUOUS REVERSAL APPARATUS

Thus far we have described machines of three distinct types, some superior in construction to others, each claiming certain advantages. However, all of them have in common one disadvantage. It is that of being of limited capacity, regardless of size, and requiring the interruption of gas inflation for refilling. This derives from the fact that the delivery tube is fixed to one chamber only and this alone can act as the gasometric chamber.

A great improvement was made when a valve was developed which can make connections alternately with either one of the chambers, or with either end of the same tube, as in the case of those models which employ a cylinder and piston. Such a valve we shall call a "commutator valve."

In the hydrostatic types, both chambers are made movable up and down in opposite direction with respect to each other, in the manner of a beam balance. First one chamber contains gas and the other liquid, then as the liquid flows from the upper to the lower, the rôles are inverted and the commutator valve makes the opportune connections with the delivery tube. Thus, a continuous, uninterrupted flow of gas is obtained without need of preliminary attention to filling or refilling the apparatus.

Grass (162) was the first to adopt this system in 1921, when he produced a continuous reversal model of the hydrostatic type. Two 500 cc. bottles are connected at the bottom by means of rubber tubing and arranged so that one lowers while the other rises. At the top, they are connected each to a limb of a four-way stopcock, while the remaining two limbs lead to a manometer and an air inlet respectively. The manometer lead is connected in parallel with the delivery tube to the needle. The different positions of the valve are controlled by means of a lever in the following manner:

(a) Lever in upright position shuts off air inlet and makes connection with the manometer and needle.
(b) One-eighth turn toward the chamber that lies at the higher level opens the air inlet and allows the liquid to flow into the lower vessel, displacing air into the delivery tube.
(c) One-eighth turn toward the lower chamber establishes a suction mechanism by the siphonage of fluid from the upper to the lower chamber. With a closed inlet, a negative pressure is created which leads to the aspiration of air from the chest.

This unique arrangement provides for continuous inflation, or suction, by just turning the lever and shifting the relative positions of the bottles.

Babajeff (163), in 1927, employing the same principle, presented an instrument which is simple and portable. It consists of a ring stand on which is fixed a cross-bar. At the extremities of this are suspended two

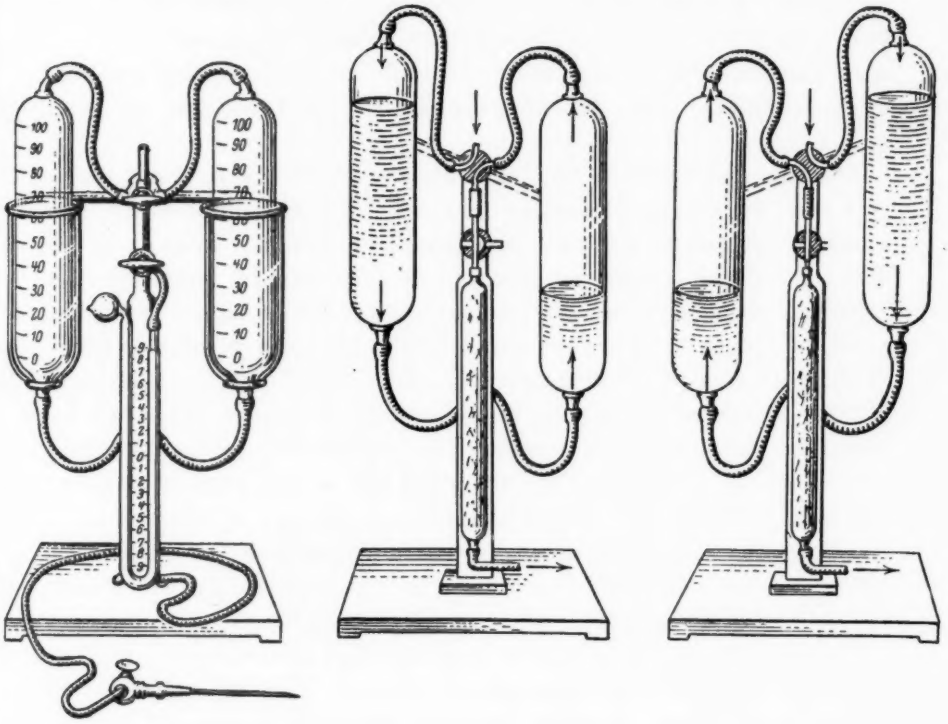


Fig. 8

BABAJEFF

graduated bottles, intercommunicating through their bottoms by means of tubing. At the centre of the cross-bar is situated a four-way valve, connected opportunely with the bottles, delivery tube, air inlet and manometer (figure 8). Tilting the bar at once raises one chamber and lowers the other and sets the valve in the proper position with respect

to inlet-outlet-manometer-needle, so that siphonage and displacement of air into the chest occur. Tilting the bar the other way reverses the connections and the relative position of the chambers, so that a continuous flow is made possible.

Davidson (164), in 1931, described a simple, compact apparatus, featuring a five-way commutator valve, operated by means of a valve stem handle (figure 9). The movements of the two reservoirs employed are controlled by a sprocket chain and their respective vertical positions are synchronized with the valve openings by the turning of the valve stem handle.

The valve provides for two differential levels of the reservoir chambers, one for initial inductions and one for refills. For initial procedures, the pointer of the valve handle is set at "initial" on the dial. The liquid in the chambers is thereby levelled and, when the needle is introduced into the pleural cavity, air is sucked in by the negative pressure. For subsequent insufflation, the pointer is set at "refill," thereby bringing the two chambers to different levels and creating a hydrostatic pressure which displaces air into the delivery tube. When the water chamber is emptied, the pointer is turned to the second "refill" and the position of the chambers is reversed, permitting a continual and limitless flow of air. A maximum pressure of 16 cm. of water can be obtained by this means. Should higher positive pressure be desired, a rubber bulb can be attached to the nipple of the air inlet to force the fluid from the higher chamber at a greater pressure.

Deflation of the pleural cavity is achieved by detaching the delivery tube and attaching it to the nipple of the inlet. The apparatus is then worked as for refills. A simple water manometer with corrected readings is employed which is placed on separate circuits, both for insufflation and deflation. Readings are obtained by turning the pointer to the appropriate marking on the dial.

Cardenas (165), four years later, described an instrument very similar to Davidson's. The manometer, however, communicates with the chest via the rubber tubing and not via the dial. It remains in circuit continually, but it may be cut out at will. Another difference is that the author provides a stop on the dial which sets the machine for suction automatically.

Edwards (166), presented an apparatus essentially similar to the Grass model.

Budge (167), at a later date, produced a modification of the Edwards ap-

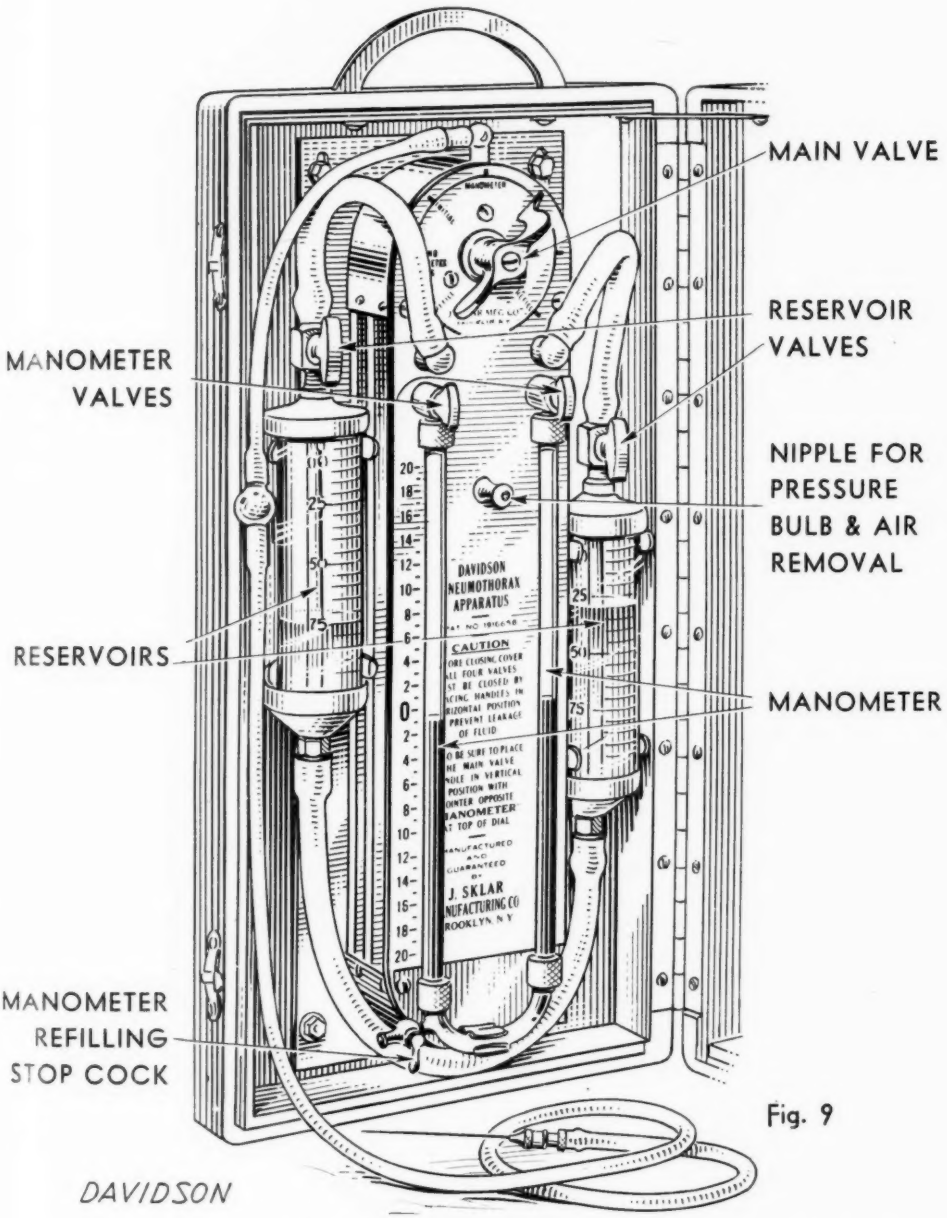


Fig. 9

paratus. The movement of the bottle is brought about by means of a clutch arrangement.

Kheyfets (168), in 1936, described another simple apparatus of the contin-

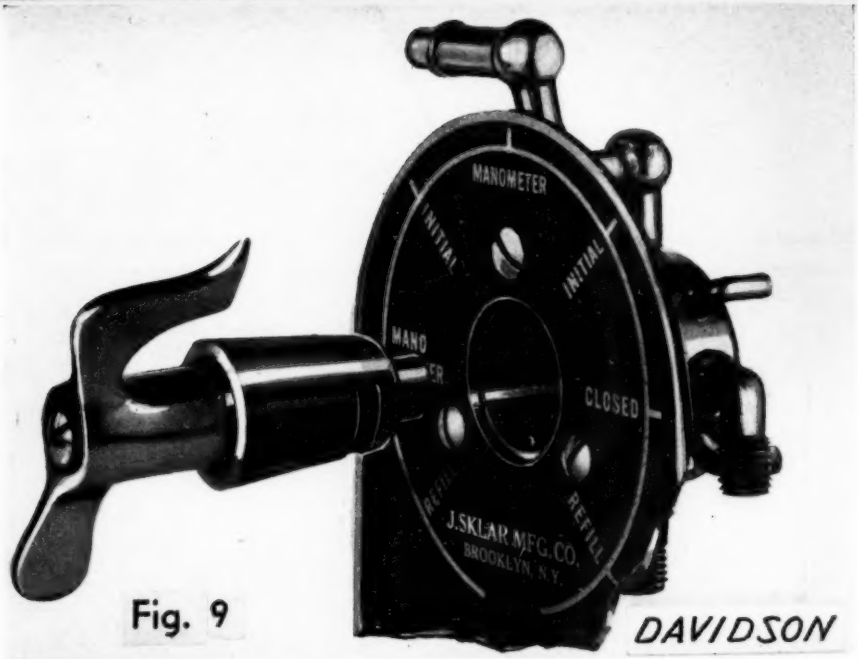
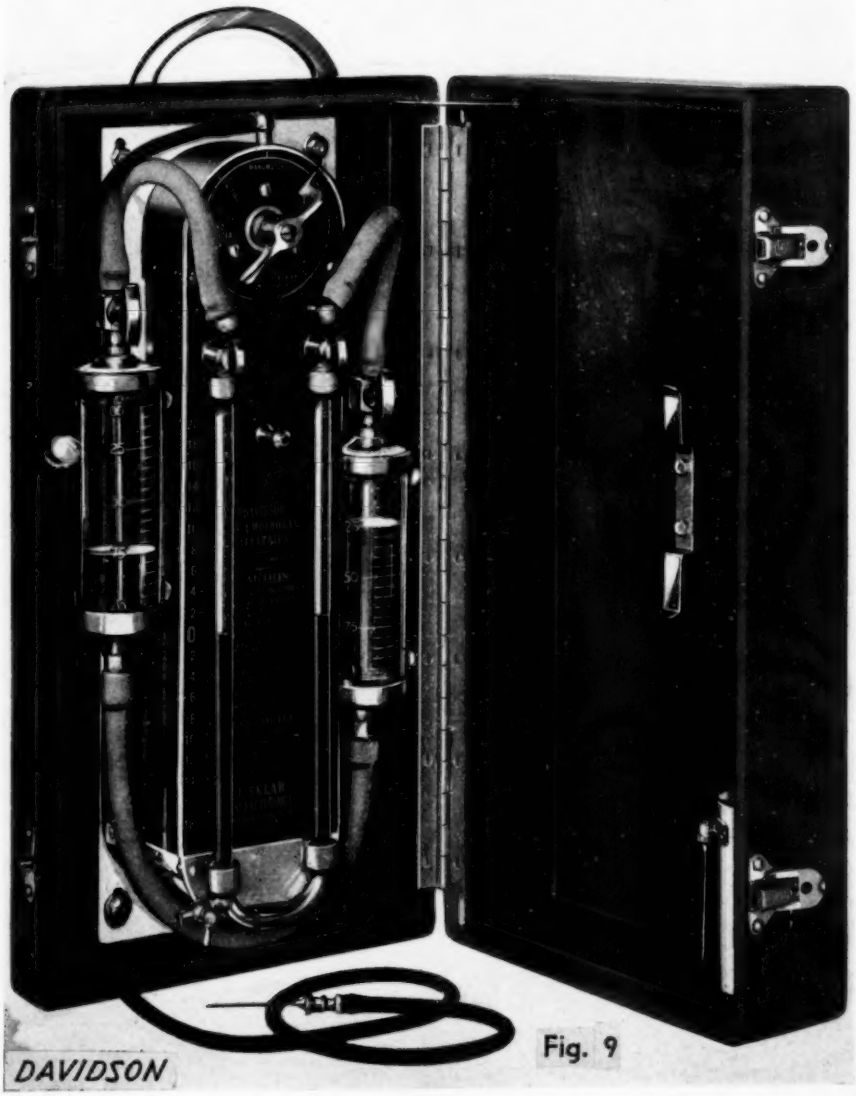


Fig. 9

DAVIDSON



DAVIDSON

Fig. 9

uous-flow type not materially different from the others, while San Vitale (169) described one very similar to the Davidson instrument.

Lloyd (170), in 1937, produced a simple continuous reversal apparatus employing the principle of the hour-glass. Two 300 cc. chambers are connected, one directly above the other, by means of a rubber stopper, provided with a specially constructed valve. The upper chamber is filled with liquid and the lower one with air. When the valve is turned on, the liquid gravitates into the lower chamber and the displaced air flows through an outlet tube into the chest and manometer. An inlet tube leads to the upper chamber. When the lower chamber is filled, the valve is turned off and the chambers simply inverted, whereupon the valve is opened, reversing the connections, and the procedure is continued. To obtain deflation, the rubber tubing is simply shifted from the outlet to the inlet lead.

Schonauer (171), in the same year, presented a variation of the hour-glass principle. The differences lay in the perfection of the details of mechanical construction. The two chambers revolve about a fixed, horizontal axis which consists of a ground glass communicator valve. In addition, there is a second stopcock valve, interposed just before the inlet tube which controls the direction of flow through the outlet and inlet, so that, by a simple turn of the key, it converts the apparatus from inflation to suction, or shuts it off completely.

The first to introduce the continuous reversal principle in the bellows type of machine was Cociasu (172) in 1922 (figure 10). This consisted of the familiar two fixed chambers and a Richardson insufflator. A commutator valve, however, made it possible to obtain a continuous flow of unlimited capacity. A simple turn of the key changes the relation of the chambers to the delivery tube so that when one is filled with fluid the other acts as gas chamber and vice versa. This machine incorporates a valve to regulate the rate of flow of the gas, and another to keep the manometer in parallel with the pleura or cut it out at will. Two manometers are used, one of water and one of mercury for higher pressures.

Kristenson (173), in the following year, described an instrument similar to that of Cociasu. He used carbon dioxide or oxygen from gas cylinders.

Zobel (174) followed with another model of this type, using another form of valve.

Duthie (175) also described one in which two valves instead of one had to be

manipulated at each reversal. Some years later he made a modification (176) but did not eliminate this disadvantage.

Basabe (177), in 1928, presented what he called a modification of Pachon's apparatus.[6] It features a valve with six openings: two leading to a water manometer, two to the delivery tube and one to each chamber. The valve is operated by means of a lever and by turning it back and forth from one position to the other and using the bellows a continuous flow of gas is obtained.

Triola's (178) apparatus, in 1928, is very similar to that of Cociasu's.

Zimmerli (179), in 1933, modified his previous instrument which permitted the refilling of liquid reservoir by turning a valve. This time he added a commutator valve, thus making it continuous reversal.

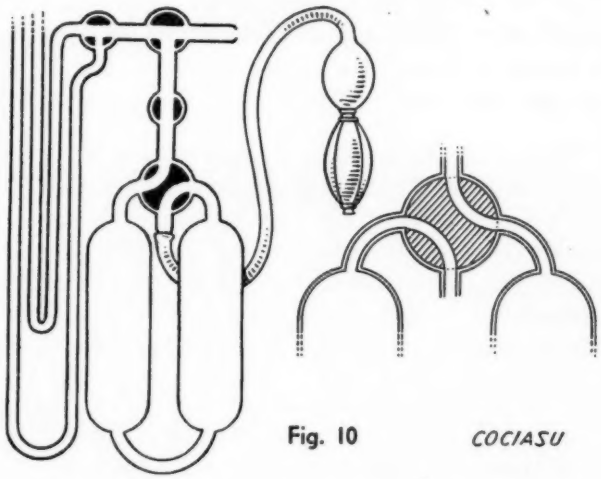


Fig. 10 COCIASU

Pisani (180) also offered a model in which two valves have to be operated for each reversal.

Thomsen (181) altered the Forlanini type and converted it into the continuous type. He used a small metal pump instead of a rubber bulb to force the fluid from vessel to vessel.

The appearance of Carpi's (182, 183) apparatus, in 1925, inaugurated this new principle in the fluid-free types (figure 11). This novel instrument features the valuable qualities of being pocketable and having unlimited capacity. It consists of a cylindrical tube of small capacity, containing a short piston of highly polished steel which moves from one end to the other, displacing 100 cc. of air with each stroke. From

[6] We are unable to find direct reference to this apparatus.

either end, two metal tubes connect it with a commutator valve, which in turn makes connection with an insufflator, a manometer and a delivery tube. Operating the insufflator and alternating the position of the valve, a pneumothorax of any capacity can be given. During the initial induction the rubber bulb is not operated and the negative pressure of the pleura is sufficient to motivate the piston for a number of strokes.

Kovats (184), at a later date, described an equally ingenious model of approximately the same dimensions, but, instead of employing a piston, he used a rubber condom inside of the cylinder. When the valve is turned in such a direction as to fill the condom, this displaces the air from the cylinder, which passes from the other extremity of the cylinder

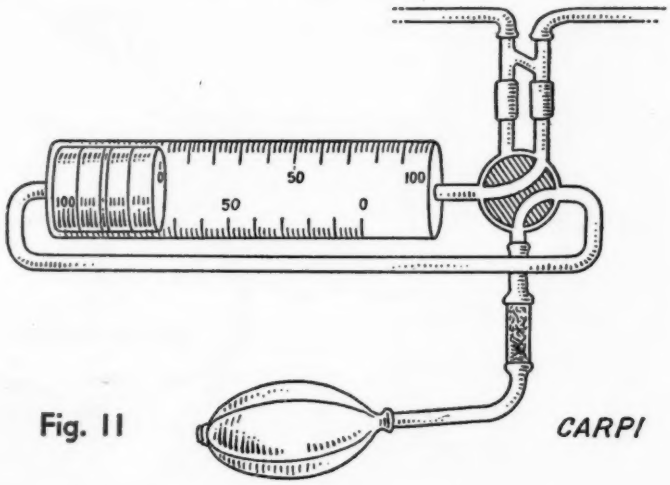


Fig. 11 CARPI

and is led through the valve to the delivery tube. Conversely, when the valve is turned, the cylinder is inflated, the sac collapses, and the air contained therein passes on into the delivery tube. A rubber bulb is used to motivate the machine. In a latter modification (185) the author substituted an aneroid manometer for the original water type; the capacity was made of exactly 100 cc. and an automatic counting device was added to record the number of strokes used. After each inflation of 100 cc. the lever automatically returned to zero, throwing the manometer into communication with the needle.

Leonet (186), in 1933, applied the same principle to a larger cylinder and perfected a machine that is very interesting indeed (figure 12). The cylinder is set on a stand in a horizontal position so that it tilts like the

cross bar of a beam balance. From each end of the cylinder connections are made with a commutator valve and through this with a manometer and delivery tube. As the cylinder is tilted to one side, the piston gravitates there and displaces a known volume of air which passes into the delivery tube and manometer. Simultaneously, the inlet tube admits air behind the piston and fills the cylinder. When tilted the other way, the valve automatically changes the connections and so maintains a continuous flow toward the chest. The manometer of the Bourdon type

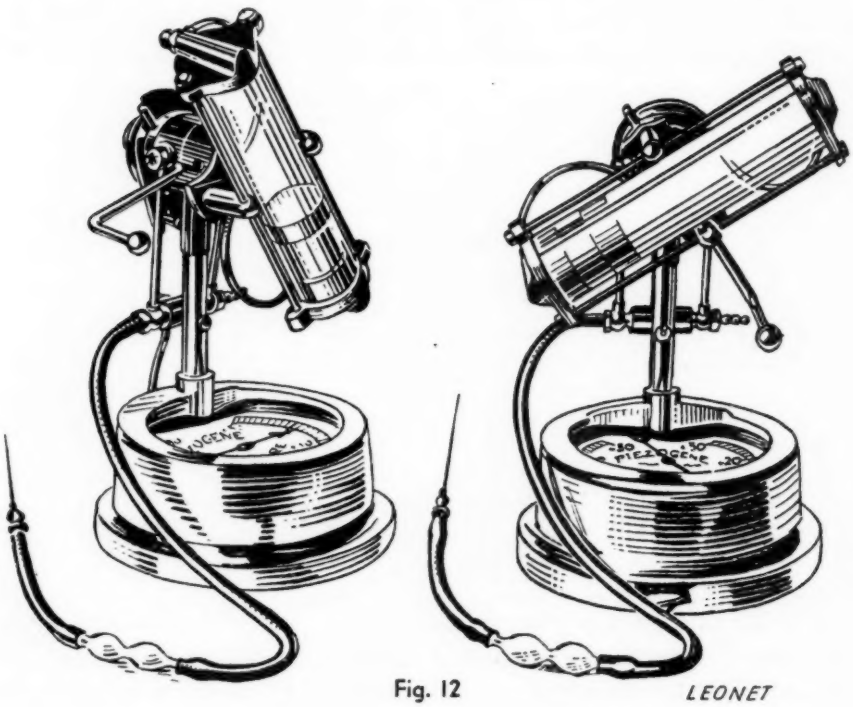


Fig. 12

is set right into the base of the stand. It is alleged to be "inertia-free" and very sensitive. The commutator valve is made of metal disks with perforations and is claimed to be free from wear and jamming. A "directional lever" changes the apparatus for deflation. The manometer is turned in automatically after each 100 cc. of air has been injected. In the horizontal position the piston is calculated to move under a differential pressure of only 2 cm. of water. This is the recommended position for initial inductions, for air is sucked and not driven into the chest.

Finally, mention will be made of an apparatus which is an interesting curiosity and which has remained to this day only of historical interest. Da-Rin (187), in 1926, described "ozone pleural therapy" and the "Pneumazon" apparatus of Firpo. This instrument featured a device for ozonating air. Air is forced by means of a pump into a metal cylinder where an electric coil, giving off sparks, produces ozone. Despite the many advantages claimed by the author, this form of pneumothorax therapy has not been mentioned again in the literature.

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SPONTANEOUS PNEUMOTHORAX[1,2]

ROBERT CHARR

In the present communication are reported 10 cases of fatal spontaneous pneumothorax with particular reference to the location of the pulmonary ruptures as found at necropsy. All cases were in the third and fourth decades of life. Six were males and 4 females. Eight had pulmonary tuberculosis, and 2 anthracosilicosis (table 1).

In all, the onset of the pneumothorax was sudden, and it occurred while the patients were in bed. In none of the cases severe coughing, sneezing or any other form of physical exertion preceded the fatal accident. The chief complaints were dyspnoea and pain in the same side of the chest as the pneumothorax. All showed cyanosis, clammy skin, weak pulse, dry mucous membrane of the mouth with thirst and apprehension of impending death.

At necropsy care was taken to find the perforation through which the air escaped causing the pneumothorax. In 7 of them the pulmonary rupture was in the midaxillary aspect of the upper lobe about 4 to 9 cm. below the apex. In 3 it was on the anterior surface about the midclavicular line. In 2 of the latter group the rupture was in the upper lobe and in one in the lower lobe about 5 cm. from the lower border of the lower lobe. The point of interest was in regard to the location of the perforations in these cases. In all the perforation was either in the front or the axillary region of the lungs. In none was the rupture on the posterior surface of the lung.

In 3 cases with the rupture on the anterior surface of the lungs, the perforation took place through the centre of large and acutely caseous tuberculous nodules, measuring about 1.5 cm. in diameter. The visceral pleura covering them was thin and transparent without adhesions to the adjacent parietal pleura. Following the ruptures deeper into the lungs led into irregularly shaped and acute cavities in the centre of caseous

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consolidation. The cavities varied in size and were located in the anterior half of the lungs. Projecting into the cavities were several stumps of bronchi and many cord-like structures criss-crossing the cavities, which on section proved to be the remnants of lung tissues. Excursion of the air through these bronchial stumps was free. When the air was rapidly pumped into the main bronchi, the perforated visceral pleura covering the caseous nodules ballooned out remarkably. The surface distribution of the caseous tubercles in these 3 cases was interesting.

TABLE 1

CASE NUMBER	NECROPSY NUMBER	PULMONARY DISEASE	SIDE OF INVOLVEMENT	LOCATION OF PULMONARY RUPTURE
1	281	Tuberculosis	Left	Axillary region of upper lobe, 4 cm. below the apex
2	333	Tuberculosis	Left	Axillary region of upper lobe, 5 cm. below the apex
3	245	Tuberculosis	Left	Axillary region of upper lobe, midway between the apex and lower border
4	311	Tuberculosis	Left	Axillary border of upper lobe, 9 cm. below the apex
5	338	Tuberculosis	Left	Axillary region of the upper lobe, short distance below the apex
6	429	Tuberculosis	Left	Anterior surface of lower lobe, 5 cm. above the lower border
7	415	Tuberculosis	Right	Anterior surface of upper lobe, midclavicular line, 5 cm. below the apex
8	462	Tuberculosis	Right	Anterior surface, midclavicular line, half way between the apex and lower border
9	454	Anthracosilicosis	Right	Axillary region of upper lobe, a short distance below the apex
10	432	Anthracosilicosis	Bilateral	Axillary region of upper lobes, near the lower borders

Practically all the acutely caseous tubercles were on the anterior portions of the lungs. The posterior parts showed principally congestion and areas of gelatinous pneumonia.

In 7 cases with the ruptures in the axillary region, the character of the ruptures differed from those already described. In none did the perforation take place through the centre of caseous tuberculous nodules as in the previous cases. There was much pleural thickening about the ruptures. The tuberculosis which was present in all excepting 2 anthracosilicotic cases was chronic in form with considerable fibrosis

throughout the lungs. Although there were scattered caseous tubercles, many of them showed, on histological examination, fibrous capsules surrounding them. Furthermore none of these cases showed superficial tubercles as acutely caseous as those in the first 3 cases.

It seems that the immediate cause of the pulmonary rupture in these 7 cases may have been tugging on the pleural adhesions. According to MacLeod (1), along the axillary aspect of the lungs there is a considerable vertical excursion of the lungs due to the comparatively greater depth of the costophrenic angle at that point. It may be on account of this that the pleural friction is more often heard on the side of the chest than anywhere else. On the anterior surface, the lung moves principally at right angles to the chest wall. In other words the sliding motion of the lung upon the inner surface of the thorax is probably most marked along the axillary aspect of the chest. Provided that this is the case, tugging movement on the pleural adhesions during respiration will be most marked along the axillary region.

The singular absence of pulmonary rupture on the posterior aspect of the lungs in the present series suggests that the cause for the apparent predilection of pulmonary rupture anterior to the midaxillary line may be largely mechanical. Due to the attachment of the ribs to the spinal column posteriorly, but to the movable sternum anteriorly, and due to the flexibility of the ribs along the lateral chest, the front and the axillary portions of the thorax move more in respiration than the posterior parts. Furthermore, when a person lies on his back, as these patients were in the habit of doing most of the time, the above factors of chest movement may be more pronounced.

In emphysema too the bulging of the thorax is more marked in front, largely due to the fixation of the costal ends to the spine. In a recent case of extraordinary bullous emphysema (2) all the blebs were on the anterior surface of the lungs and the blebs were far more numerous in the upper lobes than in the lower lobes.

In consideration of the above mechanical factors influencing the respiratory movements of the thorax, it is reasonable to surmise that the peculiar absence of the ruptures on the posterior aspect of the lungs in these cases may have been due to relatively less motion in the posterior part of the lungs, particularly in recumbent posture.

The left side is more frequently involved than the right, the percentage being approximately 60 on the left and 40 on the right (4). In the present series the pneumothorax was on the left side in 6 cases, and on

the right in 3 and on both sides simultaneously in one. Various theories have been advanced with a view to explain the left-sided preponderance. Weil (3) thought that the constant impact of the heart on the left lung made the part of the lung lying over the heart the most motile portion. Wilson (4) advanced a theory that in the normal chest the sudden systolic emptying of from 40 to 90 cc. of blood from each ventricle is compensated for by an increase in the size of the aorta and pulmonary vessels, a slight lift of the diaphragm, some shift in the position of the pericardial fluid, probably a slight shift of the mediastinum, and last, by a change in intrapulmonary pressure and some shift of pulmonary tissue immediately over the heart. This sudden change in the intrapulmonary pressure is probably to some extent distributed throughout the lungs, but that it is most marked near the heart is evidenced by the cardiorespiratory whiff so frequently heard along the left margin of the heart.

There is no doubt that the heart action produces an additional pulmonary mobility on the left side. When one gives a left-sided artificial pneumothorax refill it is not uncommon to see fairly wide oscillations of the manometer solely due to the cardiac impact upon the lung, which in turn produces variations in the intrapleural pressure.

It is generally recognized that the principal aetiology of spontaneous pneumothorax is tuberculosis. In the present series 8 had tuberculosis and 2 far advanced anthracosilicosis. The diagnosis of so-called idiopathic spontaneous pneumothorax is often disputed. But there seems to be no question that spontaneous pneumothorax does occur in diseases other than tuberculosis. In the present series 2 cases had far advanced anthracosilicosis uncomplicated by tuberculosis. Neither case showed gross or microscopical evidence of tuberculosis in either lung. Sokoloff and Farrell (5) reported 22 cases of spontaneous pneumothorax occurring among 507 anthracosilicotic patients at the White Haven Sanatorium. Of these, 14 had complicating tuberculosis and 8 pure anthracosilicosis.

Spontaneous pneumothorax in anthracosilicosis appears to be largely due to either rupture of superficial emphysema by tugging on the pleural adhesions attached to the blebs or due to gradual extension of necrosis of the anthracosilicotic mass toward the periphery of the lungs. In the present series the case with bilateral pneumothorax showed large emphysematous blebs in the midaxillary region of the upper lobes; very likely a rupture of these produced the pneumothorax. Over these blebs the visceral pleura was considerably thickened, but the microscopical examination of the walls of the blebs showed extreme thinning of the elastic

layer. In fact at several points there was an actual breach in the continuity of the elastic lamina. A severe pull by an adhesion connected to a bleb of this character may readily produce a tear with resulting pneumothorax. In the second case the perforation of the lung was due to an extension of a cavity located in the centre of a large anthracosilicotic mass in the right upper lobe. A necrosis of the central zone of an anthracosilicotic mass is not unusual. Such necrosis may form a cavity large enough to show up in a chest roentgenogram. The aetiology of necrosis is probably ischaemia. Marked pulmonary arteriosclerosis is not uncommon in the third stage of anthracosilicosis (6). In this stage the large masses of anthracosilicosis may have no blood vessels whatsoever in their centre. Due to the lack of blood supply and collection of noxious silica and coal dusts in the anthracosilicotic area, no tissue can exist. A section through some of these masses showed nothing other than piles of dust. Once a small cavity forms in the centre of such a mass, then a rapid crumbling process sets in and continues until the process is stopped by the fibrous tissue mesh almost always present about the peripheral zone of the mass where the blood supply is quite adequate. Such a process appears to have taken place in the case in question. In this the cavity was in the anterior half of the right upper lobe, and a thin channel extended laterally toward the axilla, finally perforating into the pleural cavity. There was generalized thickening of the pleura over the entire lung, but particularly about the perforation. The increased movement about the lateral part of the lung together with a possible tugging on the adhesions might have had an important effect upon the production of the rupture in this case.

An interesting pathological finding aside from those already listed was the presence of morphological changes of shock and related capillary phenomena described by Moon (7). These changes were marked diffuse congestion of capillaries and venules, especially in the lungs, liver and kidneys. Many of the alveolar spaces were filled with oedematous fluid, and the capillaries were filled with blood.

Inasmuch as both clinical and anatomical evidences of shock were present in association with spontaneous pneumothorax, it may be said that a supportive treatment usually employed in shock, in addition to withdrawal of air from the pleural space, which, of course, is most important, may be of value. Wrapping the patient with blankets in order to keep the patient warm, hot drink, oxygen and intravenous administration of fluid may be helpful. Moon warned against too much heat producing

peripheral vasodilatation and loss of body fluid in the form of perspiration, which may aggravate shock.

SUMMARY AND CONCLUSIONS

1. Ten cases of spontaneous pneumothorax were studied clinically and at necropsy.

2. In 7 the rupture causing pneumothorax was on the axillary aspect of the lungs, while in 3 it was on the anterior surface about the midclavicular line. In none was the rupture in the back of the lungs.

3. It is suggested that the apparent frequency of the perforation on the anterior surface or along the lateral aspect of the lungs in this series may be largely mechanical in that the front and the lateral parts of the thorax move more.

4. In 3 cases in which the pulmonary perforation took place through caseous nodules, the ruptures were on the anterior surface of the lungs, where the lungs move at right angles to the chest wall, and where inspiratory ballooning out of the alveoli is most marked. In 7 cases in which the ruptures were associated with pleural thickening and tugging, they were along the axillary area of the lungs where vertical excursions of the lungs are most pronounced.

5. The pulmonary rupture is said to occur more often on the left side apparently due to an increased movement of the left lung due to the heart action. In the present series it was on the left side in 6 cases, on the right in 3, and on both sides in one.

6. Tuberculosis was the aetiological factor in 8 cases and nontuberculous anthracosilicosis in 3. A rupture of emphysematous blebs and ischaemic necrosis of the anthracosilicotic mass were the immediate causes of the pneumothorax in the anthracosilicotic cases.

7. Shock syndrome with the capillary phenomenon of shock was noted in all.

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INTESTINAL TUBERCULOSIS AND CALCIUM GLUCONATE[1,2]

VITO V. PISANI

INTRODUCTORY REMARKS

Our work at the Municipal Tuberculosis Sanitarium dealing with the treatment of intestinal tuberculosis was begun in the fall of 1933. The patients diagnosed as having tuberculous enterocolitis were divided into four groups, according to the type of treatment instituted. In this paper we are concerned solely with the group designated as "group 4B," treated with intramuscular injections of calcium gluconate, 10 cc. of a 10 per cent solution. Each patient received three injections weekly over a period of time. In addition to the calcium administration, the patients received Hardt's diet, a high caloric, high vitamin and low residue diet.

Before presenting a general discussion of the subject it seems necessary to point out certain facts.

First of all, it is quite essential to recall that intestinal tuberculosis is not a disease existing by itself; it is rather a condition following and coexistent with neglected far advanced pulmonary tuberculosis. Such a consideration is of great significance when the evaluation of the results of our treatment is under discussion. In other words, it would be folly to expect from our therapeutic measures striking results in the intestinal condition, if the pulmonary lesions are not in any way controlled or are progressing. Let us bear in mind that intestinal tuberculosis is constantly influenced by the degree of activity and extent of the pulmonary lesions. As will be observed in the following pages, all treated cases displayed far advanced pulmonary tuberculosis. Another point that should be emphasized is that, for effective results, calcium therapy should be employed over a long period of time. Six months of treatment, as suggested by some, is altogether insufficient. Moreover, in view of the chronic nature of this condition and its marked tendency toward spontaneous remissions and relapses, the efficacy of any form of treatment can be properly evaluated only after a prolonged period of observation.

[1] From the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Read before the Chicago Tuberculosis Society, Chicago, Illinois, March 23, 1939.

The importance of an early diagnosis of intestinal tuberculosis cannot be overestimated. Far advanced intestinal lesions are not amenable to any treatment. The best we can hope for in such cases is the alleviation of troublesome symptoms. Many patients, who otherwise might make a good recovery, have been seriously handicapped by an unsuspected intestinal tuberculous infection.

For the evaluation of the results obtained from our investigations it must be admitted that none of the various methods of approach are absolutely accurate. Unfortunately, at the present time there exists no yardstick capable of measuring with any degree of accuracy clinical improvements. However, in the check-up, every effort was made for accuracy in determining the improvement definitely attributable to calcium therapy. Realizing that in such deductions the personal equation plays an important part, we make no claims for infallibility of judgment.

At this point, it might be well to state that, in carrying out the investigations in question, the chief purpose was that of alleviating human suffering and not of establishing a new record of achievement.

WHY CALCIUM THERAPY IN INTESTINAL TUBERCULOSIS?

Calcium in tuberculosis is still the subject of ardent controversy and the theme of numerous publications. Despite the objections and contraindications, the dogma of recalcification has been reiterated again and again. With the present knowledge of calcium metabolism we are in a better position to appreciate its sphere of usefulness and its precise indications and contraindications. In very recent years calcium therapy has received much study in keeping with increasing clinical applications, which are far beyond those of the well delimited field of deficiency diseases. The following discussion is an attempt to explain the scientific application of calcium in intestinal tuberculosis by a careful analysis of the various phenomena met with in such a disease and the correlation of the pharmacodynamic action of calcium with these phenomena.

The most important phenomena accompanying intestinal tuberculosis may be grouped under four headings:

I. Inflammatory
II. Nutritional
III. Neurogenic
IV. Reparative

I. *Inflammatory phenomena:* In all inflammatory processes the following changes stand out rather prominently:

1: Relaxation of the Rouget cells of the capillaries produced by the selective action of toxins (1)
2: Lessened cohesion between the endothelial cells of the capillary wall leading to an increased filtration of serum and colloids
3: Lowering of calcium content of the inflamed tissue (2)
4: High concentration of H-ions and reduction, of course, of oxygenation of these tissues
5: Cellular asphyxia, if these vascular changes are protracted in nature

Calcium therapy appears to be logical because:

1: It exercises a tonic effect upon the Rouget cells, thereby decreasing the inflammatory oedema and preventing extravasation of colloids (3).
2: It replenishes the tissue with the normal H-ion concentration, creating an environment less favorable to the growth and multiplication of tubercle bacilli (4).
3: It improves cellular metabolism by relieving circulatory stasis.
4: It stimulates phagocytosis. Calcium, it is well to remember, is not only a necessary element in the mineral economy of the body, but has also the important function of stimulating the defensive power of the tissue involved, manifested by an increased phagocytosis, as demonstrated by Tunnicliff (5).

No less a person than Krogh, in discussing the circulatory phenomena in inflammation, said that "calcium therapy inaugurated by Chiari and Januschke is, if rightly interpreted, to be considered as an attempt to restrain the inflammatory reactions at the point where they become harmful" (6).

II. *Nutritional changes in the intestinal tissues:* Calcium deficiency of the involved tissue together with autonomic imbalance, altered vasomotor tone and spasm lead to complete or quasi-complete stasis in a considerable number of capillaries of that particular segment of the intestine (7). Such a condition cannot but expose the tissue to grave dangers. It is difficult to see how protracted oedematous swelling of inflamed tissue can be beneficial. Calcium with its antispasmodic (8) and anti-inflammatory effect operating through the sympathetic filaments (9) relieves the tissues of the congestive phenomena, improving thereby the cellular nutrition and the elimination of metabolites.

III. *Neurogenic phenomena:* The most interesting aspect of calcium therapy in intestinal tuberculosis is perhaps that which tends to rectify the deranged physiology of the intestines. Yet such a pharmacological action of calcium has up to the present attracted very little attention.

For a clearer understanding of the basic concepts of calcium therapy, it is necessary that certain fundamental notions be explained. It might be well, therefore, to make a cursory review of that aspect of intestinal physiology which is so vital for the demonstration of the sphere of usefulness of calcium in the treatment of intestinal tuberculosis.

In the small intestine there are two main types of movements with different aims: the peristaltic and the segmentation movements. The segmentation movement is a rhythmic and churning movement necessary for the thorough mixing of the intestinal digestive juices with the chyme. The study of this movement is of great interest; it indicates the existence of a delicate nervous mechanism which animates and controls segmentation. This segmentation movement has also another important function, namely, aiding in maintaining the circulation of the blood and lymph at the normal level. Any disturbance in the rhythmic activity of the intestine will of necessity cause circulatory difficulties and poor nourishment of the tissues involved.

The nervous-nodal structure upon which such a rhythmic movement depends is known as Auerbach's or myenteric plexus. From the studies of Keith, it appears that the myenteric plexus represents a true nodal and conduction system, very closely simulating that of the heart (10). Like the heart muscle, the intestinal wall is endowed with autonomic rhythmic contractions capable of creating inner stimuli. It has been demonstrated that short segments of intestines may continue to exhibit peristaltic and segmentation movements, when immersed in a fluid containing sodium, potassium and calcium in certain definite proportions (11). Similarly, the heart of a frog may be kept beating normally for hours after removal from the body, provided it is supplied with such an artificial fluid as that just mentioned. Howell (12) has observed that "it is evident that these salts play some very important part in the production of the rhythmical beat of the heart and analysis has shown that Ca, K and Na has each its special rôle. It may be said the presence of these salts in normal proportions is an absolute necessity for maintained heart activity;" and we may add, for the intestinal activity as well.

Why this stressing of the similarity existing between the two nodal tissues, one found in the heart muscle and the other in the intestinal

wall? For one purpose, namely, to demonstrate by analogy that calcium salts, if vital to the heart's action, should be, for the same reason, vital to the functional activity of the intestines.

According to Haskell and Cantarow (13) and others "calcium dispersion ratio is found to be increased in all patients with colitis." They further assert that in such a condition, in addition to the tissue-calcium deficiency, there is also an increased capillary filtration and disturbed electrolyte equilibrium. By disturbed electrolyte equilibrium is meant a relative decrease in tissue of calcium ions in proportion to potassium and sodium ions.

The concept of the relationship of disturbances in the equilibrium of the vegetative nervous system to intestinal ulcerations is old. The consensus of those who believe in this aetiologial relationship is that ulcerative colitis is constantly associated with vagal predominance. The investigation of this phenomenon has brought into prominence certain constant tissue-changes found in association with vagotonia, among which is calcium deficiency. Zondek (14), Petersen (15), Haskell and Cantarow (16) and others have all agreed that vagotonia is constantly related to capillary dilatation, increased capillary permeability, disturbed electrolyte equilibrium with a relative decrease of calcium ions in proportion to potassium and sodium ions.

If Howell's view is accepted that a certain definite proportion of calcium, potassium and sodium is an absolute requirement for the normal function of the neural nodal tissues, and if it is agreed that in ulcerative colitis there is a coexisting tissue calcium deficiency, the need of this mineral in such cases, for the purpose of restoring the normal functional activity of the intestine, is quite apparent.

It may be argued that numerous analyses have demonstrated that blood calcium in these patients is usually within normal limits. Such an evaluation, however, is extremely misleading, and should not be regarded as a guiding norm in the application of calcium therapy.

"Blood calcium," as Noorden has well said, "does not indicate the calcium wealth or impoverishment of the tissues where the disease process takes place." The fact that local tissue variations may not be reflected in the circulating blood has been demonstrated beautifully by Rous and Drury (17), who showed that local tissue acidosis can exist, due to functional ischaemia, with no corresponding alteration in the blood reaction.

From the foregoing discussion it is not inconceivable that calcium

deficiency in intestinal tissue, with its consequent electrolyte imbalance, may disturb the delicate neural mechanism which animates and controls the peristaltic, segmentation and peridulous movements of the intestines, leading to a number of manifestations, such as loss of appetite, disgust for food, nausea at sight or smell of food, feeling of fulness after a few mouthfuls. These manifestations are thought to be due to what Alvarez (18) terms "reverse gradient," which means reverse peristalsis or anastalsis; and reverse peristalsis never occurs under normal conditions.

Calcium therapy should not be considered as a specific cure for intestinal tuberculosis, but as a rational method of restoring the normal vagal-sympathetic balance with the abolishment of intestinal spasm and its concomitant conditions.

Diarrhoea: Diarrhoea is another preëminently neurogenic symptom. The catarrhal condition of the mucous membrane lying between the ulcers, the increased irritability of the muscular coats as the results of the inflammatory process, the mechanical irritation induced by undigested food because of disturbed segmental rhythm are no doubt frequent contributing factors in the causation of diarrhoea occurring in intestinal tuberculosis. However, the most important causal factor of such a disorder is the hypermotility induced by the inflammatory changes within the nervous nodal tissue.

The myenteric plexus is often involved in the inflammatory process, although very seldom destroyed. "Consequently, the motor nervous mechanism of the intestines is rarely completely deranged, and the nerve impluses may be conducted as well as the normal tissue or even better than the normal tissue to bring about increased peristalsis" (19). Leopold's work (20) has demonstrated that in cases of diarrhoea the myenteric plexus was invariably infiltrated with round cells in addition to an extensive oedematous condition of the nerve sheaths.

Calcium salts have been used as an antidiarrhoeic drug when other means have failed, and it is believed that their beneficial effect is mainly due to their anti-oedemic action which "in spite of some contradictory evidence, is a well established physiologic fact" (21).

Pain: Pain is another neurogenic symptom of great frequency in intestinal tuberculosis. This can be explained by the increased muscular tone which interferes with Meltzer's law of contrary innervation, that is, relaxation of the distal, before contraction of a proximal portion of an intestinal segment. The relaxation fails to occur because of the state

of spasm of the affected segment. Brown (22) has remarked, "The descending wave of contraction, forcing the intestinal content before it, causes such an increase of tension, or distension, that coliky pain results, due to pressure on the nerves."

Calcium is again of some service in relieving intestinal spasm and pain in a vast majority of cases (23) by stimulating the sympathetic filaments (24) and counterbalancing thereby the state of existing vagotonia.

IV. *Reparative phenomena:* The healing of a tuberculous process, whether in the lungs or in the intestines, when it does occur, is always associated with formation of connective tissue, and sometimes with calcification. Until a biological product or a chemical substance be discovered having a specific bactericidal effect upon the tubercle bacillus, the processes of fibrosis and calcification are then the only means by which tuberculous infection is doomed. The possibility, therefore, of stimulating fibrosis in tuberculous infection, with the idea that healing would thus be accomplished, appears rational.

Recent investigations have demonstrated the indispensability of calcium in the process of fibrosis. If such is the case, then, the process of recalcification appears to be needed in order that healing be not retarded or altogether insufficient in patients who are depleted of a considerable amount of calcium because of frequent diarrhoea and because of poor absorption through the intestinal tract.

Here again, it may be pertinent to ask, what influence has calcium in fibrosis? Baitsell and Mason (25) have demonstrated by animal experimentation that the process of coagulation, apparently of the same nature as that which occurs in clotting of the blood plasma, constitutes the fundamental feature in the development of fibrils arising in the ground-substance in such conditions as wound healing and infection. If this process of coagulation identifies itself with that of blood clotting it should then depend upon the same chemical changes involved in the latter process, in which calcium seems to be absolutely necessary.

Although complete healing of tuberculous ulcers in the intestines seldom occurs, yet the marked tendency of these lesions to connective tissue formation and cicatrization is well known. The fact, however, which must be stressed is that the process of healing particularly in such cases is exceedingly slow, requiring months and even years. Because of this consideration the continuance of calcium treatment for a period of time beyond one year is urged; in fact, the longer the period,

the better. In tuberculosis, it must be remembered, cessation of symptoms is not synonymous with healing. Many months are required before such a defense reaction is carried out to its completion.

RESULTS FROM CALCIUM GLUCONATE TREATMENT

The treated cases fall into three groups:

(*1*) Definitely improved
(*2*) Fairly improved
(*3*) Not improved

Of the 43 cases, 20 were definitely improved, that is, the major symptoms, such as nausea, vomiting, diarrhoea and abdominal cramps, were unmistakably lessened in their severity, if not completely absent at the time of our final checking. Minor gastrointestinal complaints, such as flatulence, belching, pyrosis, occasional constipation, sense of fulness after eating, etc., may or may not be present; if present, they are of a transitory nature. All the patients in this group showed also an improvement in appetite, weight, strength and in general appearance.

The pulmonary lesions in these cases were found stationary or improved.

Of the 43 cases, 13 patients were fairly improved. In these cases, only an attenuation of the entire symptomatology, with appetite, weight, strength and general appearance slightly improved or unchanged, was observed. An analysis of the pulmonary lesions revealed that they were slowly progressive; evidently collapse therapy in these cases proved to be ineffective.

Of 43 cases of the series, 10 were not improved. In these patients, the onward march toward the final end was not in any way retarded. In instituting the treatment in these cases not the slightest hope of any improvement was conceived. It was fully realized that both the intestines and lungs were so extensively involved that no known treatment could ever change the course of the disease to the fatal end. Yet, these patients received their treatment because it was preferred not to do any choosing which might have created some doubts as to the effectiveness of the treatment in the improved cases.

SUMMARY AND CONCLUSION

Forty-three cases of intestinal tuberculosis were treated with intramuscular injections of calcium gluconate. The treatment extended from six to twenty-five months, having an average length of thirteen months. Of 43 patients treated, 20 were definitely improved. It cannot be over-

emphasized that the therapeutic results in such a disease can never be uniform. There are a number of variables that modify the evolution or the involution of this pathological entity, the most conspicuous of which are the tuberculous lesions of the lungs. Uncontrolled lung infection alone is sufficient to overwhelm any beneficial effect of calcium exerted upon the intestinal condition.

In comparing the clinical changes observed in patients treated with calcium and the changes seen in untreated cases, one is forced to recognize the beneficial pharmacological properties of calcium. However, in order that the results have a lasting character, it is essential that the treatment be extended beyond one year. In the course of the investigation an interesting fact was observed. A small group of patients who were improved after four to five months of treatment experienced the original gastrointestinal complaints soon after the calcium injections were by error discontinued, but they were again symptom-free or much improved after a few weeks of calcium treatment. Such a clinical observation surely indicates that the beneficial results seen in these cases were not accidental nor due to any supplemental therapeutic measures.

In conclusion, it may be said that the evidence obtained from clinical observations amply justifies the further use of calcium in intestinal tuberculosis. From the present series it is safe to draw one definite conclusion, namely, calcium in the majority of cases can bring about changes which tend to rectify the disturbed physiological activity of the intestines. Such a physiological integration makes itself apparent in the disappearance or lessening of severity of nausea, vomiting, flatulence, belching, diarrhoea or constipation, and also in the increased appetite, weight and strength. It is needless to say that in far advanced intestinal tuberculosis the neural elements are so seriously damaged as to render calcium useless. Hence the urgent necessity of an early diagnosis.

It is also important to reiterate the fact that the treatment of intestinal tuberculosis becomes doubly difficult unless the tuberculous lesions in the lung are under control.

As to the healing properties of calcium upon the intestinal ulcers, more extensive postmortem observations are needed before definite conclusions can be drawn.

Finally, the conviction that calcium therapy may be of benefit in intestinal tuberculosis is based upon the following considerations:

1. Calcium has antiphlogistic and antispasmodic properties, exerting thereby a favorable influence upon the nutritional changes in the tissues. Ulceration, be it remembered, is mainly due to such changes.

2. It restores the normal calcium ion concentration of the tissue, decreasing thereby the H-ion concentration, thus creating an environment less favorable for the growth and multiplication of the tubercle bacilli.

3. It stimulates phagocytosis.

4. It stimulates fibrosis.

5. Above all, it tends to restore the normal physiology of the intestines by counterbalancing the existing vagotonia through the stimulation of the sympathetic filaments. Such a pharmacological property alone is sufficient to place calcium as an invaluable adjunct in the treatment of intestinal tuberculosis.

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TECHNIQUE OF SPUTUM EXAMINATION[1]

Daily Studies of Sputum from Patients with Rare Tubercle Bacilli by the Dilution-Flotation Procedure and Guinea Pig Inoculation

JOSEPH E. POTTENGER

Patients carrying rare tubercle bacilli are of interest both from the diagnostic and epidemiological standpoint. This group of patients are either negative or only occasionally positive by the Ziehl-Neelsen method, although positive findings are frequently found by enrichment techniques, guinea pig inoculation or culture. Apparently little is known of the variation in daily findings in these cases by any of these methods of investigation. Daily studies of the sputum from various patients of this class over a considerable period are here presented.

PROCEDURE

Daily 24-hour specimens of sputum were collected from selected patients who had shown tubercle bacilli intermittently on previous occasions by the dilution-flotation picric acid technique (1). The patient was instructed to save everything that was raised, including postnasal and pharyngeal mucus if present. Each specimen was homogenized in a mechanical shaker for ten minutes, and a portion (2 cc. or more) was removed for protein and cell-volume[2] determinations. The remaining sputum was digested at 55°C. for thirty minutes with equal parts of 0.5 per cent sodium hydroxide; or if the specimen was large, a sufficient amount of 20 per cent sodium hydroxide was added so that the resultant strength of sodium hydroxide was 0.25 per cent. The mechanical shaker was now employed again and the digested specimen was centrifugalized lightly at 1,000 r.p.m. for two minutes to throw down excess epithelium and food remnants. The supernatant solution was removed and treated by the dilution-flotation method.

[1] From the Laboratory of the Pottenger Sanatorium, Monrovia, California.

[2] The cell volume is the measurement of the cell content. The sputum is homogenized by shaker, and a portion is placed in a special centrifuge tube which is kept at 50° C. for twenty-four to thirty-six hours. The cells are then compressed by centrifuge, at 37°C., 3000 r.p.m. for thirty minutes. The cell volume is then determined by proportion.

In the series (table 2) where both dilution-flotation and guinea pig inoculation were used, the treatment was as follows: after adding the digestant and shaking for five minutes the specimen was set at 37°C. for two hours to lessen the virulence of the contaminators; after shaking for ten minutes the specimen was centrifugalized lightly as above, and the upper third removed for the dilution-flotation test; the lower two-thirds, together with the residue from the first fraction, was neutralized with acid with brom-thymol blue as indicator and injected into a guinea pig. Two-thirds was inoculated intraperitoneally and one-third in the left axilla.

All animals were tuberculin tested before inoculating with 0.1 cc. PPD second strength. Retesting was done about the twentieth day after inoculation and repeated every three to five days up to the thirty-fifth day. A final test was made about the sixty-fifth to seventieth day.

CLINICAL CONDITION OF PATIENTS WHOSE DAILY RECORDS OF MICROSCOPIC FINDINGS ARE TABULATED IN TABLE 1

Seven of the 13 patients presented in table 1 had shown strongly positive microscopical findings on entrance to the sanatorium. The remaining 6 patients reported that bacilli had never been found before entering, so that the microscopical diagnosis was of much importance, although all showed lung markings by X-ray except Miss M. S. Mr. J. U. stated that 30 examinations had been made during the last four years, always with negative result. Miss M. S. entered with a report of negative microscopical findings, but positive culture. Tubercle bacilli had been demonstrated microscopically once before this record was made. Mrs. G. W. had enlarged cervical nodes, with minimal roentgenological changes in the lung. Tubercle bacilli had been demonstrated twice microscopically before the daily record was made. Miss E. B. had bronchiectasis, and tuberculosis was not considered until rare bacilli were found. Guinea pig tests were previously positive in all these patients. All of the 13 patients were afebrile at the time of examination.

SENSITIVITY OF THE DILUTION-FLOTATION METHOD

In order to determine the sensitivity of the dilution-flotation technique, proved negative specimens of sputum ranging in amount from 1 cc. to 20 cc. were selected. To each specimen were added 10,000 ± tubercle bacilli; they were then homogenized by shaker and treated by the dilution-flotation technique. The number of tubercle bacilli recovered in a

TABLE 1

Daily record of sputum examinations of 13 patients by the dilution-flotation technique

PATIENT	INITIAL DATE	NUMBER OF DAYS EXAMINATIONS WERE MADE																				AVERAGE IN CC.	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Sputum	Cell volume
Mr. H. M.....	4/21/32	0	1	5	3	2	1	6	1	1	20	4	3	12	1	1	2	2	4	30	2	25.0	1.8
Mr. J. U.....	4/ 2/32	0	0	4	1	1	1	0	14	8	1	6	1	4								10.3	0.4
Mrs. L. T.....	4/16/32	0	2	7	5	0	6	27	0	12	37	0	10	12	4	6	10	10	3	5	9	3.5	0.1
Mr. G. B.....	1/14/32	1	1	2	2	1	0	2	0	3	1	173	6	1	0	0	0	0	2	0	0		
		2	2	1	0	1	0	0	14	0	1	0	0	1	4	6	10	0	0	0	5		
		0	0	0	0	1	2	20	0	6	0	5	0	2	4	2	1	5	0	5	2	9.3	0.3
Miss R. M....	7/14/32	0	0	0	0	0	1	0	1	0	1	0	0	0	0	32	4	2	1	0	0	10.6	0.3
Mrs. J. M.....	3/21/36	1	2	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	1	0	0		
		0	0	0	0	0	0	1	0	0	0	0	0	2	3	1	0	0	0	1	5		
		0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	1	0	0	0	4	3.2	0.16
Mr. C. N.....	5/31/32	0	0	0	0	0	0	0	1	0	0	0	0	3	1							19.0	0.4
Mr. E. T.....	10/ 2/32	0	NS	0	0	1	0	1	0	0	0	0	NS	0	0	0	0	0	2	0	3	4.0	0.08
Mr. W. J.....	8/31/37	0	NS	0	0	0	138	0	0	2	0	0	0	NS	0	0	0	0	3			0.6	0.03
Miss E. B.....	5/ 2/32	1	0	0	0	1	0	0	0	0	0	0	1	4	0	0	0	0	0	0	0	202.0	31.0
Mr. I. M.....	6/17/37	0	0	0	3	0	0	0	0	0	0	0	0	0	4	0	0					11.0	0.3
Miss M. S....	10/ 5/35	0	0	3	0	0	NS	0	0	0	0	0	0	0	0	2	0	0	0	0	NS	4.0	0.06
Miss G. M....	8/ 6/37	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				5.0	0.1

Numerals arranged in rows represent the number of tubercle bacilli found in a ten-minute search by dilution-flotation.

NS means no sputum was raised.

The last two columns of figures give the average amounts of sputum and cell volume for each patient for a 24-hour period.

ten-minute search was recorded. From this information two ratios were determined, one expressing the sensitivity per cc. of natural specimen and the other the sensitivity per cc. of cell volume. An actual record will illustrate the method: Sputum 27387, 5 cc., cell volume 0.31 cc., 9 bacilli recovered in a ten-minute search.

Therefore, $\frac{10{,}000 \text{ bacilli}}{5 \times 9} = 222$ bacilli per cc. necessary to yield one bacillus in a ten-minute search, and $\frac{10{,}000 \text{ bacilli}}{.31 \times 9} = 3{,}600$ bacilli per cc. of cell volume necessary to yield one bacillus in ten minutes' search.

The average result from 37 specimens with tubercle bacilli added gave the following: One bacillus in a ten-minute search indicates the presence of 173 $\pm$ 61 tubercle bacilli per cc. of natural specimen and 4,000 $\pm$ 1,650 tubercle bacilli per cc. of cell volume. The range of sensitivity in various specimens is of course wide, as shown by the probable errors.

Ten of the 13 patients averaged less than 12 cc. of sputum daily, and 11 of the 13 less than 0.5 cc. of cell volume daily, so that one bacillus found in a ten-minute search indicates the presence of about 2,000 bacilli or less in the 24-hour specimens from these patients.

The efficiency of the dilution-flotation method with picric acid as counterstain, as compared with the direct smear stained by methylene-blue, will vary within wide limits unless the material is thoroughly homogenized by mechanical shaker before the preparations are made.

Schoub (2) was the first to show by reasonably accurate methods that picric acid will reveal 5.7 times as many bacilli in the same time of search as can be found with methylene-blue. The writer (1) reported 5.3 times as many in homogenized material. These two factors agree closely.

Some years ago the concentration factor attained by the dilution-flotation technique was determined as follows. Specimens of positive sputum were shaken thirty minutes and a film was made. The remaining sputum was treated by the dilution-flotation method. A film was placed on the same slide as the direct film, and stained simultaneously both counterstained with picric acid. Per field counts gave an average of 14.7 times the number of bacilli by flotation as by homogenized smear. The superiority of the dilution-flotation picric acid method over the homogenized smear counterstained by methylene-blue should then be $14.7 \times 5.5 = 80$ approximately, so that since 100,000 tubercle bacilli per cc. of purulent sputum are necessary for demonstration by the

Ziehl-Neelsen method (Corper), only $\frac{100{,}000 \text{ bacilli}}{80} = 1{,}250$ bacilli per cc. would be necessary for demonstration by the flotation method. In practice, because of the much greater water content and small amount of pus, in many natural specimens a correspondingly smaller number of tubercle bacilli may be detected.

DAILY VARIATIONS IN RESULTS BY THE DILUTION-FLOTATION METHOD AND GUINEA PIG INOCULATION

All specimens were examined for likely particles, but in general the pus was diffusely scattered and efforts at direct smear usually resulted in failure. One patient, Mr. G. B., furnished typical particles occasionally in which bacilli were found by direct film with picric acid counterstain. On the sixth day of the investigation of Mr. W. J. a typical particle was found, giving 8 tubercle bacilli in a ten-minute search in direct smear. A microflotation test was performed on the remaining portion of the particle giving 138 bacilli in a ten-minute search, which represents a 17.2 times superiority for flotation.

In table 1 tubercle bacilli were found 118 times and, accepting 80 as the approximate factor of superiority of flotation with picric acid as counterstain over Ziehl-Neelsen with methylene-blue as counterstain, most of these positives, except Mr. G. B. eleventh day, and Mr. W. J. sixth day, would likely be negative by Ziehl-Neelsen.

Table 2 gives the result of the daily animal inoculation of the sputum of 8 patients, 4 of whose records are given in table 1. The result of the guinea pig inoculation for each specimen is expressed by a plus or minus sign. The numerals immediately above each plus or minus sign represent the number of tubercle bacilli found in a ten-minute search by the dilution-flotation method, while the numbers in parenthesis give the number of tubercle bacilli found in a thirty- to ninety-minute search. The letter F means failure of the animal test due to early death from other causes. Twelve animals of a total of 183 were lost. Fifty-seven, or 33.3 per cent, of the remaining guinea pigs were positive, so that of those that died early four would be expected to be infected had they lived. While this loss is regrettable it does not alter the general conclusion. For statistical purposes these failures are considered as negative in result. NS means that no sputum was raised.

The record of Miss M. S. was made from two-day specimens because of

TABLE 2

Daily record of the inoculation of guinea pigs with sputum and correlation with findings obtained by the dilution-flotation technique

PATIENT	METHOD OF EXAMINATION	NUMBER OF DAYS EXAMINATIONS WERE MADE																				MAXIMUM NEGATIVE INTERVAL
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
																						days
Mr. I. M.	D.F.	0	(0)	(2)	3	0	0	0	0	(0)	(0)	(0)	(1)	(0)	(4)	(1)	(2)					
	G.P.	−	+	−	+	F	−	−	−	+	+	+	+	+	+	+	+					4
Mrs. J. M.	D.F.	1	2	0	0	(2)	0	0	(2)	0	0	0	0	(1)	2	(2)	0	0	1	0	(1)	
	G.P.	+	+	+	−	+	−	−	+	−	−	−	−	+	+	+	−	−	+	−	+	
	D.F.	0	(4)	0	0	0	0	1	(2)	0	(3)	0	0	4	3	2	0	0	0	1	5	
	G.P.	−	+	−	−	−	−	+	+	−	+	−	−	+	+	+	−	−	−	+	−	
	D.F.	0	(1)	(1)	0	0	0	3	0	0	(3)	(0)	(0)	0	0	0	1	0	0	0	4	
	G.P.	−	+	+	−	−	−	−	−	−	+	+	+	−	F	−	+	−	−	−	−	6
Miss B. K.	D.F.	0	(0)	0	(0)	0	0	(0)	(0)	0	0	0	0	0	0	(0)	(1)	(0)	(0)	(2)		
	G.P.	−	−	−	−	F	−	+	+	F	−	−	−	F	F	+	+	+	+	+		6
Mr. W. J.	D.F.	(0)		0	(0)	0	138		0	2	0	0	(0)		(0)	(1)	0	(0)	3			
	G.P.	+	NS	−	−	−	+	−	−	+	−	−	−	NS	−	+	−	+	+			5
Mrs. G. W.	D.F.	0	0	(0)	0	(0)	0	(0)	0	(0)	(0)	0	0	0	0	0	(0)					
	G.P.	−	+	−	−	+	−	+	+	−	+	−	−	−	−	−	−					6
Mr. R. P.	D.F.	0	0	0	0	(1)	(0)	0	(0)	0	0	0	0	0	0	0	0	0	(0)			
	G.P.	−	−	−	−	+	−	F	+	−	F	F	−	−	−	−	−	−	+			9
Miss G. M.	D.F.	0	3	0	(0)	0	0	0	0	(0)	0	0	0	0	0	0	0	0	0			
	G.P.	−	+	−	−	−	F	−	F	−	F	−	−	−	−	−	−	−	−			15
Miss M. S.	D.F.	0	0	0	0	0	0	0	0	NS	NS	0	0	0	0	0	0	0	0	0	0	
	G.P.	−	−	−	−	−	−	−	−			−	−	−	−	−	−	−	−	−	−	
	D.F.		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	G.P.	NS	NS	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	
	D.F.	0	0	(1)	(1)			0	0	0	0	0	0	(0)	(0)	0	0	0	0			
	G.P.	−	−	−	−	NS	NS	−	−	−	−	−	−	+	+	−	−	−	−	NS	NS	
	D.F.	0	0																			
	G.P.	−	−																			52

G.P. = guinea pig, followed by result as + or −.
F = failure of test.
NS = no sputum.
D.F. = dilution-flotation.
Numerals indicate number of bacilli found in a ten-minute search.
Numerals in parentheses indicate number found in prolonged search.

the small amount of sputum raised. The last column of table 2 gives the maximum time for each patient during which the guinea pigs were negative.

Tubercle bacilli were found five times, although the corresponding guinea pigs were negative: Mr. I. M., third day; Mrs. J. M. fortieth, forty-seventh and sixtieth days; and Miss M. S., twenty-third and twenty-fourth days combined. Fifty-seven guinea pig tests were positive, as compared with 18 positive flotation tests in a ten-minute search, and 39 positive flotation tests by prolonged search (thirty to ninety minutes).

TABLE 3

Computation of number of tubercle bacilli in the 24-hour specimen from selected records found in table 2

PATIENT	QUANTITY SPUTUM	DAY EXAMINED	RESULT FLOTATION	COMPUTATION	NUMBER BACILLI 24-HOUR SPECIMEN
	cc.				
Mr. I. M.....	10.0	15th	1 bac. 60 min.	$\frac{10 \times 173}{6}$ =	289
Mrs. J. M.....	1.5	13th	1 bac. 90 min.	$\frac{1.5 \times 173}{9}$ =	29
Mr. R. P.....	13.0	5th	1 bac. 70 min.	$\frac{13 \times 173}{7}$ =	321
Mrs. G. W.....	1.0	5th	Negative 60 min.	$\frac{1.0 \times 173}{6}$ =	29
Miss M. S.....	1.5	53rd–54th	Negative 40 min.	$\frac{1.5 \times 173}{4}$ =	60

It is evident that some of these specimens contained but a few bacilli as shown by the following records, and the computed number of bacilli for each specimen. All guinea pigs in this group were positive.

Since no bacilli were found in the films from the last two specimens (table 3), we have a reasonable expectation that the actual number of bacilli present were less than the computed number.

INADEQUACY OF GUINEA PIG INOCULATION FROM 24-HOUR SPECIMENS

Table 4 shows the relative value of inoculations from specimens saved for one day, three days, etc., up to fifteen days, for diagnostic purposes. It gives the total possible inoculations of various consecutive day periods

D.F. = dilution-flotation.
Numerals indicate number of bacilli found in a ten-minute search.
Numerals in parentheses indicate number found in prolonged search.

that can be arranged from the record of each patient in table 2. For instance in the record of Mr. I. M. the first three-day period in which the result is certain would be first day, second day, and the day previous to the experiment, positive result; the second three-day period would be first day, second day and third day, positive, then second, third and fourth, positive, etc., up to the last certain result which would be found in the three-day periods sixteenth day, seventeenth day and eighteenth day. By inspection the total number of possible periods and the number of positive results for each are determined.

TABLE 4

Comparative efficiency of inoculations from sputum collected for various time periods from data found in table 2

PATIENT	THEORETICAL AMOUNTS OF SPUTUM PER INOCULATION																	
	1-day			3-day			5-day			7-day			9-day			15-day		
	Total inoculations	Positive inoculations	Per cent positive	Total inoculations	Positive inoculations	Per cent positive	Total inoculations	Positive inoculations	Per cent positive	Total inoculations	Positive inoculations	Per cent positive	Total inoculations	Positive inoculations	Per cent positive	Total inoculations	Positive inoculations	Per cent positive
Mr. I. M.....	16	10	62.5	17	15	88.2	19	19	100	21	21	100	23	23	100	29	29	100
Mrs. J. M.....	60	24	40.0	60	48	80.0	60	58	96.7	62	62	100	64	64	100	70	70	100
Miss B. K.....	19	7	36.8	19	11	57.9	19	15	79.0	19	19	100	21	21	100	27	27	100
Mr. W. J.....	18	6	33.3	20	15	75.0	22	21	95.5	24	24	100	26	26	100	32	32	100
Mrs. G. W.....	16	5	31.2	15	11	73.3	15	13	86.7	15	15	100	17	17	100	23	23	100
Mr. R. P.....	18	3	16.7	18	9	50.0	18	13	72.2	27	17	85	22	21	95.5	28	28	100
Miss G. M.....	17	1	5.9	16	3	18.7	16	5	31.2	16	7	43.7	16	9	56.2	16	15	93.7
Miss M. S.....	62	2	3.2	60	4	6.7	58	6	10.3	56	8	14.3	54	10	18.5	54	16	29.6
Totals.....	226	58	25.5	225	116	51.6	227	150	66.1	233	173	74.2	243	191	78.6	279	240	86.0

This tabulation indicates that only 25.5 per cent of the one-day periods are positive. Three-day periods double the efficiency to 51.6 per cent, and fifteen-day periods give 86 per cent.

Willis (3) recommends the use of a seven-day inoculum, although the positive results obtained were 7.8 per cent less than were obtained by a fourteen-day inoculum.

SUMMARY AND CONCLUSION

A report on the examination of successive twenty-four-hour specimens of sputum by the dilution-flotation picric acid method and guinea pig inoculation is presented. Of a total of 171 specimens, 57 were positive

to guinea pig; 18 were positive in a ten-minute search after treatment by dilution-flotation; and 39 were positive after prolonged search (thirty to ninety minutes).

The dilution-flotation technique will detect tubercle bacilli in a ten-minute search if present to the extent of about 175 per cc. of natural specimen. Below this number the guinea pig is advisable for diagnostic purposes.

Guinea pig inoculation if negative is wholly inadequate for diagnosis, if only a 24-hour inoculum is used. In a group of 8 patients in which a definite diagnosis of tuberculosis had been made only 25.5 per cent of the specimens were positive in guinea pigs. A statistical study shows that a three-day inoculum would be positive in 51.6 per cent; and a five-day, seven-day, nine-day and fifteen-day inoculum in 66.1, 74.2, 78.6 and 86 per cent, respectively.

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CLINICAL AND LABORATORY NOTES

TENSION PNEUMOTHORAX[1]

WILLIAM A. ZAVOD

Tension pneumothorax or valvular pneumothorax can occur on the basis of trauma, tuberculosis or pulmonary suppuration, and it is characterized by a valvular communication between a bronchus and the pleural cavity. The valvular mechanism is such that air can enter the pleural cavity but cannot escape from it.

The purpose of this paper is to describe the observations on a case of tension pneumothorax that was studied clinically during the entire period of the operation of the valve and an investigation of the structure of the valvular mechanism at the postmortem table.

F. L. was a white man, 24 years old, who was first admitted to the Grasslands Hospital in 1931. He had, at that time, a minimal tuberculous process in the left lung for which pneumothorax was instituted in April, 1931. The treatment was effective, the sputum became negative and the pneumothorax was continued in the clinic until April, 1935 when reëxpansion was approved. The lung was completely reëxpanded by October, 1936. He refused to return to the clinic for periodic follow-up examinations and was not seen until July, 1937 when he came to the clinic complaining of recurrence of cough and expectoration. Fluoroscopic and roentgenographic examinations showed new caseous infiltration in the upper half of the right lung with early cavitation. The left lung was reëxpanded and showed no evidence of new disease. Pneumothorax on the right side was instituted in the clinic, a free pleural space was found and the treatment was continued until September 3, 1937 when a

FIG. 1. F. L. September 20, 1937. Roentgenogram showing pneumothorax on the right with multiple peripheral thin-walled cavities. Displacement of the heart and mediastinum to the left, pneumatocele in the left hemithorax, pneumonic infiltration in the lower half of the left lung.

FIG. 2. F. L. Posterior view of the right lung before inflation; small opening with smooth edges seen at the base of the upper lobe near the interlobar septum.

FIG. 3. The same lung after manual pressure is applied to the inflated left lung, while the trachea is clamped off. Note the increase in size of the fistula.

[1] From the Tuberculosis Division of the Grasslands Hospital, Dr. R. M. Franklin, Acting Chief of Service, Valhalla, New York.

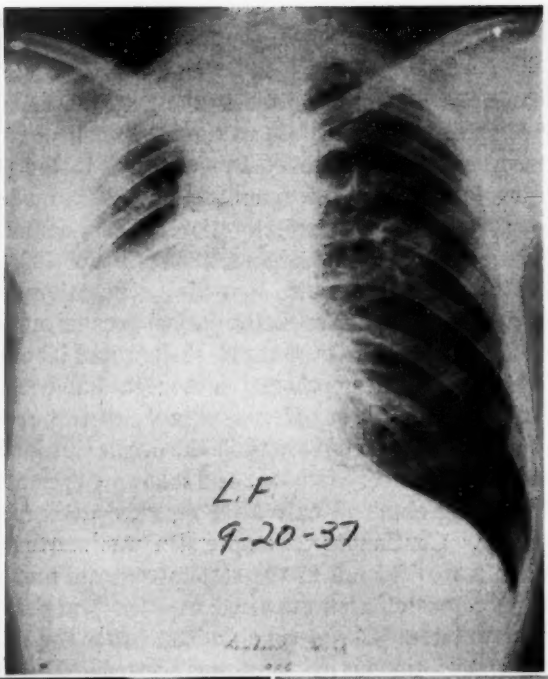

FIG. 1

FIG. 2

FIG. 3

bed was available and he was admitted to the hospital. At this time there was evidence of spread of the disease to the lower half of the left lung and rapid progressive excavation of the caseous process in the partly collapsed right lung (figure 1). He had a temperature of 102°F., moderate dyspnoea, distressing cough and copious expectoration. The pneumothorax on the right was continued at the bedside, he received refills of 200 to 300 cc. twice a week and the intrapleural pressures were always negative. On October 16, 1937, following a severe coughing spell, the patient became markedly dyspnoeic and cyanotic. His respirations were rapid, shallow and labored. It was evident that the therapeutic pneumothorax on the right had become complicated by a tuberculous pneumothorax. He was decompressed but the intrapleural pressure continued to build up rapidly while the needle was in the chest cavity. The attacks of cough were very frequent and following each attack he became moribund, relief being obtained only after repeated decompression of 1,500 to 2,000 cc. of air. Continuous decompression was started that afternoon which resulted in a marked fall in the respiratory rate and general clinical improvement. A serous effusion appeared the following day and it became purulent three days later. Closed tube drainage after the method described by Franklin (1) with continuous irrigation was started. The valvular mechanism was evidently constantly in operation since the dyspnoea and cyanosis reappeared every time the draining tube was clamped off or became plugged with exudate. Cough would force large amounts of air through the draining tube into the water bottle. The patient was becoming weaker and more toxic and expired November 2, 1937. The outstanding and most debilitating symptom was cough that was not relieved by repeated doses of codeine.

Excerpts from the autopsy report: External examination revealed a thoracotomy wound one cm. in diameter in the sixth interspace in the anterior axillary line. The contents of the thoracic cavity were removed *in toto* with the parietal pleura intact; 300 cc. of thin yellowish pus was removed from the right pleural cavity through the thoracotomy opening in the parietal pleura. In order to study the operation of the valvular fistula, the right pleural cavity was filled with water and moderate manual pressure was applied over the pleural sac while the mass of thoracic content was suspended with the trachea downward. Careful examination showed no evidence of water leaking from the pleural cavity into the bronchi and trachea. Gentle inflation of the lungs with air through the trachea showed a brisk bubbling of air through the water in the pleural cavity. Manual pressure upon the inflated left lung with the trachea clamped off showed a similar bubbling of air through the water in the pleural cavity. The parietal pleura over the right lung was then incised and reflected. A thin layer of fibrin lined the parietal and visceral pleurae. A herniation through the anterior weak zone was seen extending into the left hemithorax. There were no adhesions. Examination of the right lung showed

a small opening at the base of the upper lobe (figure 2) which, upon inflation of the lung by pressure on the left lung and trachea closed, became an opening measuring about one cm. in diameter (figure 3).

Section of the right lung showed several thin-walled cavities distributed in a cluster along the periphery of the upper lobe. The fistula was found in the peripheral wall of one of those cavities and a bronchus measuring about 4 mm. in its largest diameter opened into the cavity wall opposite the fistula. Dissection from the bronchial opening inward showed free communication with larger bronchi. The remainder of the lung showed multiple large caseous foci undergoing rapid liquefaction.

The parietal pleura of the left lung was moderately thick. Upon incision, 100 cc. of clear serous fluid rich in fat globules was found in the pleural cavity. The left lung was free from apex to base anterolaterally and loosely bound to the parietal pleura posteriorly. Section of the left lung showed multiple large caseous foci in the lower two-thirds. No cavities were seen. Fibrous scars were found in the upper third. The tracheobronchial tree revealed marked congestion and moderate thickening of the mucosa, no ulcerations were evident grossly. The thoracic lymph nodes were enlarged, tuberculous, but not caseous.

Comment: The mechanical principle of a simple valve is such that air or liquid can pass in one direction only. The structure of the valve embodying this principle can vary. It can be in the form of a flap, a slit or a purse-string arrangement.

The flap valve: This type is most likely to occur in an incomplete tear of an adhesion at the point of insertion into the pulmonary parenchyma. Cutler (2) reported several cases of spontaneous pneumothorax complicating therapeutic pneumothorax in whom the valvular fistula closed after pneumonolysis. He expressed the opinion that the complication was due to an incomplete tear of an adhesion, though he gave no visual thoracoscopic proof or necropsy control to substantiate it.

The slit valve: This type is most likely to occur in stab wound to the lung or longitudinal laceration of the lung by the point of a needle during pneumothorax therapy or aspiration of pleural fluid, when the pulmonary tissue is in opposition with the needle point and is cut during respiration.

The purse-string valve: This valve is an ulcerative opening from the outer wall of a peripheral cavity into the pleural space. This type is most frequently encountered in progressive caseous pulmonary tuberculosis and occasionally in pulmonary suppurative disease.

The first two forms are, no doubt, sound possibilities, though, to my knowledge, no proved case has been recorded in the literature and I have not come across one in my autopsy material. The third type is reported in this paper.

The valvular mechanism is seldom seen at the postmortem table because in most cases in which the tear occurred in healthy or nonactively diseased pulmonary tissue the closure of the valve and recovery are spontaneous. In others, where the disease is progressive, the tension pneumothorax disappears by the time of exitus and at the postmortem table a nonvalvular bronchopleural fistula is found. It may be logical to assume that progressive ulceration enlarged the original valvular opening that caused the tension pneumothorax to a size where the purse-string mechanism is no longer in operation and the fistula is permanently open.

The interpretation of the mechanism of a tension pneumothorax must be sought in the sudden rise in the intrapulmonary pressure during strain and cough, as was suggested by von Muralt (3) and by Fenichel (4). Immediately following the formation of a valvular fistula, the involved lung will pump air into the pleural cavity until the intrapleural pressure is atmospheric or slightly above. If the lung is free of adhesions it will collapse and the valve will close. During cough, however, the intrapulmonary pressure rises to 70 to 100 mm. of mercury (an experiment that can be easily performed with a sphygmomanometer), the glottis is momentarily closed immediately before cough, the high pressure is transmitted through both lungs and the valve is forced open to admit air into the pleural cavity from the surrounding pulmonary tissue and from the contralateral lung. Grunting, talking and straining at stool also raise the intrapulmonary pressure with similar results. The contributing factors are: herniation of air into the contralateral hemithorax with displacement of the heart and mediastinum when these structures are flexible, compression of the opposite lung, torsion of the heart and large blood vessels and interference with circulation. When the mediastinum is rigid, interference with circulation results from the high pressure on the heart and blood vessels. These phenomena lead to labored, rapid respirations, cyanosis, drying of the mucous membranes and more distressing cough. Thus a vicious circle is established which is broken either by permanent closure of the valve, or by progressive enlargement of the fistula until the valvular mechanism disappears or death intervenes.

SUMMARY

A case of tension pneumothorax with autopsy control is reported. The various types of valves are listed. The mechanism of the purse-string valve is illustrated and discussed.

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ILEOCAECAL TUBERCULOSIS[1]

Diagnosis by a Direct Double Contrast Method of Roentgenological Examination of the Small Intestines and Colon (Enteroclysis)

J. GERSHON-COHEN AND HARRY SHAY

Double contrast barium enteroclysis is a method of direct roentgenological examination of the small intestines which lends itself to a rapid diagnosis of ileocaecal tuberculosis. The diagnosis rests on the same roentgen findings obtained by serial barium-meal and barium-enema examinations. These findings are often more definite because filling of the small intestines is generally completely uniform. For these reasons, we have come to regard barium enteroclysis as another useful method to establish the roentgen diagnosis of ileocaecal tuberculosis.

TECHNIQUE

The examination is done with a duodenal tube, a water-barium suspension and air. After the tip of the tube has come to rest beyond the second portion of the duodenum the opaque barium suspension, injected by gravity or by a hand syringe, progresses through the entire small intestinal tract and colon much more rapidly than when administered orally; the head of the column of opaque contents reaches the caecum in from five to fifteen minutes. It is not necessary to resort to special preliminary stimulation of the small intestines with hypertonic salt solutions or to cleansing with castor oil, as recommended by Ghelew and Mengis (1). (A nice control over the filling of the jejunum and ileum can be had through the use of a transfusion syringe to transfer the opaque contents from an Ehrlenmeyer flask to the tube leading into the intestines.)

Some reflux into the proximal duodenum and cap may occur because of the position of the duodenal tube but, if the pressure of the injected material is not raised too high, the pylorus will prevent regurgitation into the stomach. The tip of the duodenal tube can be brought through the pylorus by the Morgenstern (2) method, sometimes in a few minutes. It takes 400 to 800 cc. to visualize the small intestines and then the right colon begins to fill without adding more opaque suspension; the head of the column often reaches the splenic flexure before halting. When air is injected, as in the double-contrast studies, smaller quantities of the opaque suspension are needed. The visualization of the margins of overlapping intestinal coils is easier in the double than

[1] From the Eagleville Sanatorium, Eagleville, Pennsylvania.

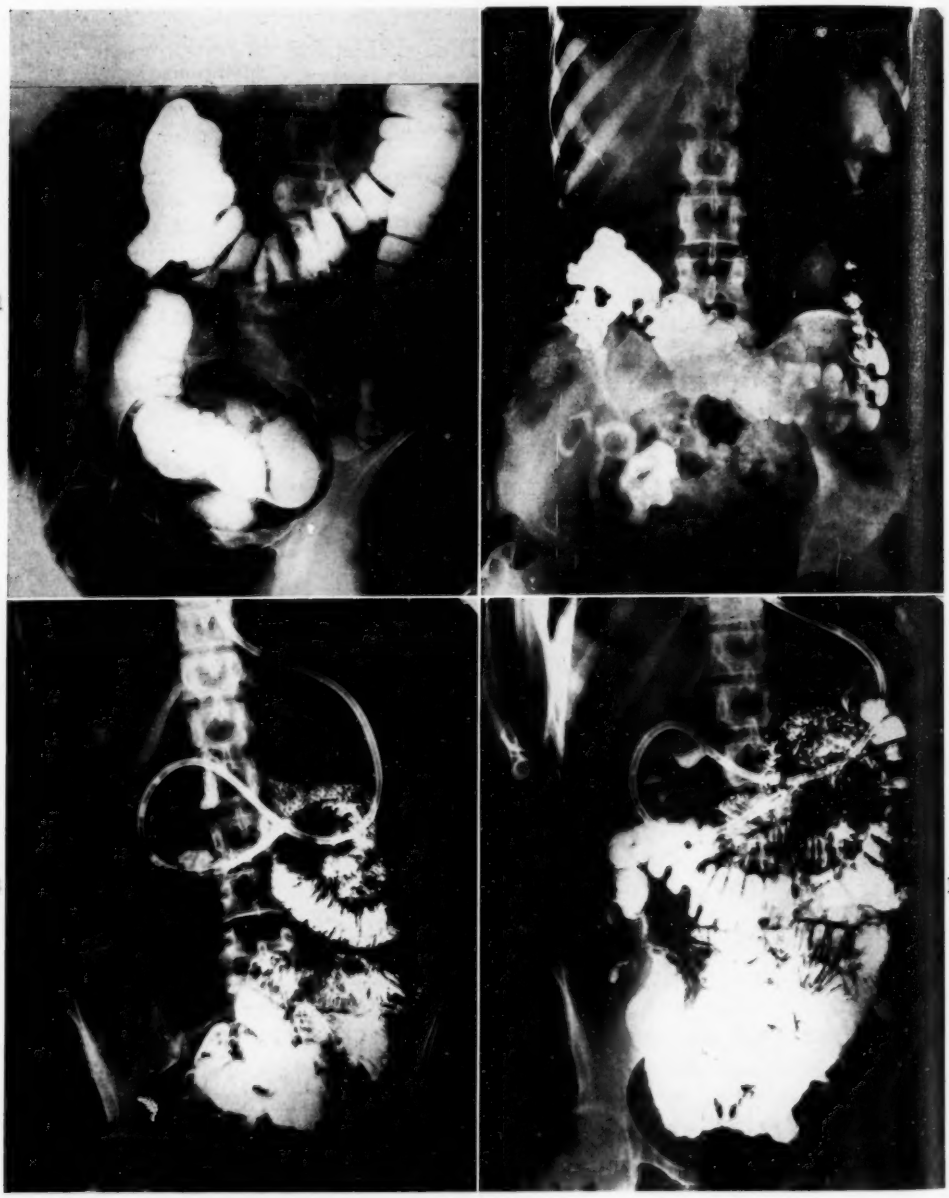

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIGS. 1–4

in the single-contrast films. Air is injected by the same transfusion syringe used for the opaque contents and the amount used is just enough to fill the intestines without undue distention and without discomfort to the patient. "Spot" films or other roengtgenographic records may be made depending upon what best suits the case.

DISCUSSION

Many attempts have been made to develop some method of direct roentgenological visualization of the small intestines. Pesquera (3) has already pointed out the advantages of this rapid visualization for tuberculous lesions of the small intestines and we have been able to confirm all his findings. Shiffer (4), in his Master's thesis for the University of Pennsylvania, discussed thoroughly the studies of the duodenum made roentgenographically and added a worthy contribution of his own in his use of the Miller-Abbott tube. In some studies of pyloric action recently done by us, we observed a more efficient competency of the pylorus when the duodenum was filled than we expected as well as an unusually rapid filling of the entire small intestinal tract. These observations led us to try application of this technique to the roentgen study

FIG. 1. Double contrast enema examination. This reveals an irregular stenotic lesion in the lower right colon. The terminal ileum is dilated even though this film was made after bowel evacuation. The wide spacing of the *valvulae conniventes* in the ileum gives it the appearance of a segment of colon; thus the lesion resembles a "napkin-ring" cirrhotic malignant process of the colon. The patient was sent into the hospital because of symptoms suggesting intestinal obstruction and, because the barium enema examination was the first done, it was difficult to rule out malignancy as the cause of symptoms until after the other studies had been made.

FIG. 2. Film made four and one-half hours after progress water-barium meal. The pseudo-filling defect in the ileocaecal area is apparent, but the exact extent and character of the pathological process are not visualized.

FIG. 3. Double-contrast barium enteroclysis, after injection of 400 cc. water-barium suspension and sufficient air to dilate those coils already traversed by the opaque suspension. This film was made six minutes after the beginning of the examination. By carefully avoiding pressure high enough to cause incompetency of the pylorus, reflux into the stomach was prevented.

FIG. 4. This film was made eight minutes after that in fig. 3. A total of 800 cc. of water-barium suspension had been used and more air inflated to fill both the small and large intestines already traversed by the barium suspension. The head of the injected column of contents has advanced to the splenic flexure. The canalized terminal ileum, the obliterative contraction of the caecum, and the short segment of colon distal to the ileocaecal valve are all nicely shown. Since lesions so extensive, involving the terminal ileum, caecum and ascending colon, are rarely malignant and since such lesions are characteristic of tuberculosis, this diagnosis was made and subsequently held to be even more likely by the finding of bilateral pulmonary fibroulcerative tuberculosis.[2]

[2] Patient referred by Dr. R. E. Brant, and, since this report, patient has been operated by Dr. W. E. Burnett at Temple University Hospital where the roentgen findings were confirmed.

of the small intestines, especially for ileocaecal tuberculosis—one of the lesions nicely demonstrated by this method when the barium-meal or enema examinations are not entirely satisfactory. The chief handicap of the procedure is that not all patients can swallow a duodenal tube, and it is particularly difficult for those with laryngeal tuberculosis.

CONCLUSION

A method for double-contrast visualization of the small intestines is described which is applicable to a rapid diagnosis of ileocaecal tuberculosis.

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A SEROLOGICAL REACTION IN TUBERCULOSIS[1]

JOHN B. WEST[2] AND RUTH M. EASTERLING[2]

Viewing with some concern the uncertainty of the value of physical methods for the diagnosis of tuberculosis, and realizing that the Mantoux reaction with tuberculin is efficient in the determination of tuberculosis infection but not in the diagnosis of tuberculosis disease, we are brought face to face with the need for an accurate means of serodiagnosis. In our attempt to produce this diagnostic aid, however, we are often prone to rely too strongly on laboratory methods, almost to the exclusion of clinical diagnosis. Obviously, the laboratory cannot supplant the clinician, and laboratory results must be considered as corollary evidence to be accepted in light of clinical findings. In our fight against disease one might well say that the sword of laboratory diagnosis must be tempered with the fire of clinical wisdom.

HISTORICAL

Following many more or less successful attempts at serodiagnosis, Hinton (1), in 1930, proposed a cholesterol agglutination reaction which he considered very promising. In a series of 18 known positive cases of tuberculosis, he obtained 16 frank positive serological reactions and 2 doubtful. On the other hand, in a series of 107 presumably negative cases, from Boston Lying-in Hospital, he found only 2 that presented positive serological reactions. One of these 2 carried a tentative diagnosis of suspected tuberculosis, but no subsequent report has been available on either of the 2 cases.

TECHNIQUE

Following the lead offered us by Hinton in his work we have attempted to clarify in our own minds some of the problems entering into the intricacy of serodiagnosis of tuberculosis. We obtained stock cultures of living strains of H37 and R1 from Doctor Hinton, and an unknown strain from Phipps Institute. All three strains were cultured on both Sauton's medium and on Long's synthetic liquid medium. While Hinton records that neither of these media showed any superiority over the other, it was our experience that Long's

[1] Published with the permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

[2] City of New York Department of Health, Central Harlem Health District, New York City.

synthetic liquid medium was preferable, in that it produced more rapid and more luxurious growth.

The three strains of organisms were grown on the two media for a period of seven weeks, after which the liquid was filtered off through fine paper at room temperature, under atmospheric pressure. The residue of live bacilli was washed three times with sterile distilled water, each washing being equal in volume to that of the medium filtered off. The moist bacilli were then placed in a 55°C. incubator where they were allowed to remain for four days to dry thoroughly and kill the organisms.

At the end of four days the bacilli were weighed, and extractions made after the method described by Hinton, consisting of extracting each of the three strains with four separate portions of ether (Squibb, for anaesthesia). Each extraction involved the use of eight volumes of ether for each part by weight of bacilli. During each extraction the flask was vigorously shaken for ten minutes.

After the fourth ether extraction, the residue was dried at room temperature and weighed. The ether-insoluble residue was then extracted with five volumes of 95 per cent ethyl alcohol for each part by weight of residue.

It was our experience that this method resulted in an antigen not quite as promising in specificity or sensitivity as some derived from other methods of extraction, the most satisfactory of which in our experiments was as follows: Seven volumes of ether (Squibb, for anaesthesia) were added for each part by weight of dried bacilli. The suspension was shaken for fifteen minutes, after which time the bacilli were allowed to settle out, leaving a rather milky supernatant fluid. The ether was filtered off and saved for evaporation. This procedure was repeated until a total of five extractions had been made, giving a grand total of thirty-five volumes of ether for each original part by weight of bacilli. The last extract was practically clear. Then the alcoholic extraction was performed according to Hinton's method. This final antigen was pale, straw colored, clear and sparkling.

For the actual serological tests that followed, we believe that the best results were obtained with a mixture of nine parts of 0.6 per cent solution of cholesterol in absolute ethyl alcohol to one part of bacterial antigen.

Similar methods of extraction followed in which we used liver obtained from a patient who had died of miliary tuberculosis. (The parenchyma of this liver was studded with miliary tubercles.) It was ground fine, dried on a glass plate at 55°C. for four days and weighed. The extractions were made according to those previously described by us. The resulting antigen was entirely unsatisfactory.

In the production of cholesterinized antigen, which we called after Hinton's nomenclature "antigen, modified," we added nine parts of the 0.6 per cent solution of cholesterol in absolute ethyl alcohol to one part of antigen derived from

dried tubercle bacilli, and from this point we followed Hinton's outline for the preparation of what he elects to call "glycerinated indicator." The procedure was to add two parts of 5 per cent solution of salt (Merck, C.P.) to one part of antigen, modified. This mixture was vigorously shaken for one minute, and then twelve additional parts of salt solution were added with a second shaking for one minute. This mixture was allowed to stand ten minutes, and fifteen parts of 50 per cent glycerine (Arthur H. Thomas, redistilled, neutral) were added, with a third shaking for five minutes. This glycerated indicator proved quite unstable, and was useless twenty-four hours after it had been mixed.

TABLE 1

SYPHILIS				TUBERCULOSIS DIAGNOSIS			
Number of Sera	Wassermann	Hinton	Kahn	Clinical	X-ray	Sputum	Serology
109	Negative	Negative	Negative	Active	Positive	Positive	Positive
16	Positive	Positive	Positive	Active	Positive	Positive	Positive
24	Negative	Negative	Negative	Active	Positive	Negative	Positive
3	Positive	Positive	Positive	Active	Positive	Positive	Doubtful
9	Negative	Negative	Negative	Negative	Positive	Negative	Positive
14	Negative	Negative	Negative	Inactive	Positive	Negative	Negative
4	Negative	Negative	Negative	Inactive	Positive	Negative	Positive
Negative Controls							
210	Negative	Negative	Negative	Negative	Negative	Negative	Negative
116	Positive	Positive	Positive	Negative	Negative	Negative	Negative
1	Positive	Positive	Positive	Negative	Negative	Negative	Positive
1	Negative	Negative	Negative	Negative	Negative	Negative	Positive

The sera were inactivated at various temperatures and for different periods of time, but the most promising results were obtained with sera inactivated at 55°C. for fifteen minutes. Wassermann tubes were set up in series of three rows. Inactivated sera were pipetted into the tubes as follows: 0.1 cc. in front row, 0.3 cc. in the second row, and 0.5 cc. in the third row. To each of these tubes 0.5 cc. of glycerinated indicator was added. The tubes were shaken for three minutes at 250 oscillations per minute. The tubes were incubated at 37.5°C. for sixteen hours, and then read.

The reading of these reactions, like the reading of the Hinton glycerol cholesterol reaction for syphilis, is among the least difficult of serological interpretations. In cases of known tuberculosis there was marked clearing of the fluid with massive clumping of the particles of cholesterol, producing the effect of a small coagulum of egg albumen in hot water. In the less strongly

positive sera clearing was not so marked, and the particles appeared as large granules, similar to the result of a moderately positive Kahn reaction. The negative reactions were opalescent, with no evidence of clearing or clumping. In two series of presumably negative cases a white ring appeared at the meniscus, but in each tube the ring was quickly dispelled by gentle agitation. Table 1 gives a summary of our results.

DISCUSSION

From table 1 it will be observed that of 161 serological tests on cases diagnosed as active tuberculosis clinically, by X-ray, by sputum or by some combination of the three, all were positive except 3, which were doubtful. Of 18 cases diagnosed as inactive tuberculosis 4 gave positive reactions, and the remainder, negative. In this connection it is interesting to note that in Hinton's series of 18 cases of known tuberculous disease only 2 were doubtful and none was negative.

Further in a series of 328 examinations of control sera drawn from presumably nontuberculous patients, only two showed positive reactions with tuberculosis antigen. One of these cases (Reg. #9765) also presented positive syphilitic serology. This patient carried an X-ray interpretation of moderate calcification and fibrosis in the region of the hilum. The other (Reg. #9845) was admitted with a clinical diagnosis of extensive trychophyton infection and pellagra. A diagnosis of tuberculosis had not been made. Subsequent examination failed to reveal clinical, X-ray or laboratory evidence of tuberculosis.

In the two series there was no apparent correlation between tuberculous and syphilitic serological reactions, while the clinical and serological manifestations were in accord in more than 90 per cent of the known tuberculous cases, and in less than 1.0 per cent of the 328 presumably negative cases were false positive reactions obtained.

As was the case in Hinton's experiments, we found that antigens made from different strains gave different reactions with certain sera. For instance, in one case of known active tuberculosis the antigens from H37 and R1 gave negative reactions, while the antigen from the unknown strain obtained from Phipps Institute gave a strongly positive reaction.

Lest an incorrect interpretation of our findings be made, we feel we should note here that among our 500 serological reactions, often two or three were performed on the same patient, so that, although our number of examinations totals 500, only 260 individual patients were included in the experiments.

SUMMARY AND CONCLUSION

Based on the serological studies of Hinton (1, 2, 3) and others, we have conducted this investigation in an attempt to determine some of the factors involved in a serological diagnosis of tuberculosis. It is to be borne in mind

that this is a preliminary report of our experiments, and is of necessity incomplete. Much additional laboratory research is necessary before the value of this type of diagnosis for tuberculosis can be definitely calculated. The authors feel that this small series but serves as an indication of what may be expected in a larger series, and that standardization of the antigen and of the technique will result in greater correlation of clinical and serological findings. With that ultimate goal in mind, we hope to continue our work in the future.

We wish to express here our sincere appreciation to Dr. William A. Hinton for providing us with stock cultures of bacilli and for his interest and assistance in carrying on this work, and to Phipps Institute for the contribution of cultures without which our progress would have been greatly impeded. We wish, too, to thank the Veterans Administration and Dr. J. H. Ward for providing us with the laboratory facilities and for their permission to use the sera of patients hospitalized at the Veterans Administration Facility at Tuskegee, Alabama.

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BACTERIOSTATIC POWER OF SERUM IN PULMONARY TUBERCULOSIS[1]

WILLIAM A. KREIDLER AND CHRISTIAN W. NISSLER

Observations indicating that the sera of patients suffering from pulmonary tuberculosis may possess a varying amount of bactericidal substances were reported a few years ago by Courmont and Gardere (1). More recently Courmont and Moulinier (2) have emphasized the importance, among other tests, of the bactericidal power of the patient's serum in prognosis. They state that "Curves plotted during the course of the disease in the acute, localized forms which are rapidly cured by pneumothorax treatment indicate the increased resistance of the patient and the progress of treatment. The progressive elevation of the bactericidal power as well as of the agglutinating titre signifies an excellent prognosis; and conversely, if they decrease during the course of pulmonary tuberculosis the prognosis is unfavorable:—a fatal outcome may follow within several months." Our observations on a small group of cases are in agreement with Courmont and his associates which fact leads us to present them in this paper.

PROCEDURE

Sputum obtained from the patient was digested with sulphuric acid and seeded on Loewenstein's medium. After incubation at 37°C. good growth usually appeared in two or three weeks. Colonies were classified with regard to various degrees of roughness.

When the cultures were to be used for serological work, 5 cc. of physiological salt solution was added to the slant and the growth scraped off with a stiff wire. This suspension was transferred to a tube containing glass beads and shaken in a mechanical shaker for one hour. Of this homogeneous suspension 0.1 cc. was used to inoculate each of a series of tubes containing various dilutions of patient's serum in Long's synthetic medium. The dilutions used were 1:10, 1:20, 1:50 and 1:100. A tube of this medium without serum and one with 1 cc. of normal serum served as controls. The series of inoculated tubes was incubated at 37°C. At the end of a month a final observation of each tube was made. The growth was recorded as: −, +, ++, +++ or ++++. Results of inhibition of growth are recorded in table 1.

[1] From the Departments of Bacteriology and Diseases of the Chest, Jefferson Medical College and Hospital, Philadelphia, Pennsylvania.

RESULTS

Of the 23 cases included in our study, there were 7 patients whose sera showed no inhibitory action on the growth of the acid-fast bacterium isolated from the sputum of the patient concerned. Of these, 5 died, one is worse and one shows no improvement. There were 8 persons whose sera showed only slight inhibitory action and, of these, 4 died, 3 showed no improvement and one is slightly improved. Thus, of this group of individuals with little or no

TABLE 1

NUMBER	GROWTH INHIBITION	NUMBER	GROWTH INHIBITION
1	Moderate	19	None
2	Very slight	20	Moderate
3	None	21	None
4	None	22	Very slight
5	Very slight	25	None
5 (one year later)	Moderate	26	Very slight
7	Moderate	30	Slight
13	Moderate	33	None
15	Very slight	34	Moderate
16	Moderate	35	Very slight
17	None	36	Slight
18	Slight	37	Moderate

None = when average growth in the serum tubes was ++++.
Very slight = when average growth in the serum tubes was +++.
Slight = when average growth in the serum tubes was ++.
Moderate = when average growth in the serum tubes was +.

TABLE 2

NUMBER OF PATIENTS	INHIBITORY REACTION OF SERUM	NUMBER DIED	NUMBER SHOWING NO IMPROVEMENT	NUMBER WORSE	NUMBER IMPROVED
7	None	5	1	1	0
8	Slight	4	3	0	1
8	Moderate	0	1	2	5

bacteriostatic substances in their sera 71.5 per cent died. In Courmont and Gardere's (1) similar study of 77 cases, a mortality rate of 45 per cent was reported. Also, in those of their group that showed marked inhibition, there was a mortality rate of 13.3 per cent. None of our patients showed marked inhibition, but the serum of 8 persons exhibited moderate bacteriostatic power. Of these, 5 showed improvement, one is unimproved and 2 are worse but none has died. (See table 2.)

In our series of 23 patients, all but one were far advanced cases of pulmonary

tuberculosis. The one exception was only moderately advanced. The cases have been under our observation two years or longer.

The present study seems to indicate that those patients whose sera show little or no bacteriostatic action have an unfavorable prognosis; evidently they would be poor risks for surgical procedures. Mortality rate in this group is high. Those who have a moderate or marked inhibitory serum action have a better prognosis and are better surgical risks. That bacteriostatic action of their sera can change was shown in one of our patients; thus the test should be repeated from time to time and a curve plotted. Obviously such a curve is of more value than a single determination of the bacteriostatic or bactericidal activity of serum constituents.

There is another observation that is of interest. All of our cultures of *Mycobacterium tuberculosis*, which were made from sputa of patients with pulmonary tuberculosis, were R (rough) strains. While there were varying degrees of roughness we did not obtain any strains comparable in characteristics to S strains of other microörganisms. Textbooks usually give the impression that the S strains of *M. tuberculosis* are the most virulent type in spite of the fact that R forms are usually isolated from active, far advanced cases. We are inclined to agree with the recent work of Alexander-Jackson (3) and others that virulent strains usually isolated from active cases of the disease are intermediates with varying degrees of roughness rather than true S colonies in the strict sense in which the term "S" has come to be used.

CONCLUSIONS

Mycobacterium tuberculosis has been isolated from 23 cases of active pulmonary tuberculosis in pure culture.

The technique is described for investigating the inhibitory effect of substances in the patient's serum on the strain of the acid-fast microörganism found in the sputum.

We feel that such tests along with agglutination and complement fixation reactions for tuberculosis are not only helpful in determining the prognosis but are also valuable in making decisions regarding surgical procedures.

It is believed by the authors that the test here described will indicate the resistance of the patient against the particular strain of *M. tuberculosis* causing his infection.

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THE TUBERCULIN TEST[1,2]

Its Value and Its Limitations

ESMOND R. LONG

The symposium of which this paper is a part has been organized to review the procedures employed in mass surveys for the discovery of cases of tuberculosis, and at the same time to afford discussion of certain problems within this field that have arisen in the course of surveys recently conducted.

It would lead us too far afield if I were to attempt a discussion of all the questions at issue in my own particular assignment, the tuberculin test, and I shall therefore confine my remarks to the problems that have raised the most grave concern in recent months. The queries and doubts that have arisen within the last two years have had a healthy effect on our antituberculosis campaign in forcing us to review our current procedures and test the validity of past beliefs. It is to the credit particularly of the United States Public Health Service and other official agencies that certain concepts too lightly accepted in the past have been subjected to reinvestigation.

It is with such considerations in mind that I have affixed the subtitle, the value and limitations of the tuberculin test, to this paper. I shall attempt to discuss the larger rather than the incidental problems of the tuberculin test in case-finding, and shall omit certain issues that might carry us off from the main problem of tuberculin testing as a general procedure. I shall not discuss the merits of the different kinds of tuberculin on the market, nor shall I attempt a comparison of results to be obtained by the various methods of conducting the tuberculin test, not because the problems concerned are unimportant, but because their discussion might distract attention from the larger aspects of the question. In what I have to say I shall have reference only to the intracutaneous test and to the two kinds of tuberculin most commonly used, Old Tuber-

[1] Presented at a Symposium on *Mass Tuberculin Testing and X-raying* at the 35th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, June 29, 1939.

[2] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

culin and the Purified Protein Derivative tuberculin; this course is justified because the queries to which I shall refer are the consequence of experience based on this method and these tuberculins. I shall also refrain from extended discussion of the tuberculin test as an index of the total amount of infection and direct my remarks to the test as a means for finding cases of tuberculosis.

I shall define this term later. First, however, it will be wise to review briefly some facts on the test and its application.

GENERAL PRINCIPLES IN TUBERCULIN TESTING

The tuberculin test has an extensive background. In the early nineties of last century Robert Koch discovered that guinea pigs infected with tubercle bacilli regularly became sensitive to extracts of the bacilli. A correlation between tuberculosis and tuberculin sensitivity was promptly established in man and cattle, but it soon developed that other animals might not exhibit tuberculin allergy after the development of tuberculosis.

As far as I know, the tuberculin test is practically infallible in guinea pigs. Doses of tubercle bacilli sufficient to cause progressive tuberculosis appear to lead invariably to tuberculin sensitivity. To be sure, this may wane with the arrest of lesions, on the one hand, or with the development of profound cachexia, on the other, as the terminal stage is approached. But during the intervening period tuberculin sensitivity is as characteristic as any phenomenon in the field of immunology.

Tuberculin allergy in cattle has been the subject of but little question in recent years. The success of the campaign for eradication of bovine tuberculosis, based, as it is, on the tuberculin test, is a strong empiric argument for the practical value of the test. More tangible evidence for its specificity and adequacy, however, occurs in the almost constant finding of tuberculous lesions in cattle slaughtered because of a positive tuberculin reaction, and the failure to find tuberculosis in the routine inspection of millions of cattle not reacting and killed for meat production. The well known "no-lesion reactor" constitutes an exception, but from the point of view of immunological science not a serious one, for in this case infection with a related microörganism seems to be concerned.

In certain other animals, however, tuberculin allergy is far less conspicuous. It is only under exceptional circumstances or by special means that tuberculous rats and mice are found to be tuberculin-sensitive, and rabbits and monkeys, although subject to a type of tuberculosis not

greatly different from that seen in guinea pigs, show a tuberculin allergy that is feeble and inconstant in character.

These brief considerations naturally raise the question of the place of man in the scale of tuberculin allergy. Until recently his extraordinary sensitivity, rather than his occasional anergy, has been stressed. The rapid growth of programs for testing man has now furnished us with an abundance of data, from which we may draw conclusions on both phenomena. It has long been known that human beings may be exquisitely sensitive, reacting severely to exceedingly minute fractions of a milligram of tuberculin. On the other hand we now know that cases are occasionally found in which good evidence for the presence of tuberculosis exists, although the tuberculin reaction is either extremely weak or even entirely negative.

This is not the place for extended discussion of the correlation between strength of the reaction and character of existing tuberculosis in man, but a few brief comments should be made. Most surveys fail to disclose an obvious correspondence between size of reaction and extent of disease. However, certain types of tuberculosis do lead to excessive sensitivity. Tuberculosis of the lymph nodes or bones, with extensive caseation, commonly causes high sensitivity. Negroes, other factors being equal, appear to react more strongly than whites. In frank pulmonary tuberculosis the reaction is ordinarily weaker than in the case of well controlled recent infection without clinical disease. Finally, if our experience at the Henry Phipps Institute may be accepted as an index, the strongest reactions are given by young adults in apparent good health, but heavily exposed to infection.

Unfortunately the question of tuberculin sensitivity in man can never be studied with the same scientific thoroughness as in guinea pigs or cattle, which can be infected and slaughtered at will. However, a development of recent years, BCG vaccination, has enabled us to study the results of artificial infection and its relation to tuberculin sensitivity on a large scale. The results of Park and Kereszturi, indicating an almost constant development of tuberculin allergy following vaccination, are well known. To them I would like to make brief addition from the experience of a colleague, Dr. J. D. Aronson, now with the United States Indian Service, who has under way a BCG vaccination program involving nearly three thousand children, half of them vaccinated and the other half controls. His results will be reported in detail later, but with his permission I may note here that, of 1,482 previously tuberculin-negative

children vaccinated with BCG, 1,383, or 93.3 per cent, were positive a year later. Of 1,312 children of corresponding age, also tuberculin-negative at the start of observation, but not vaccinated, only 167, or 12.7 per cent, became positive within the year. It is presumed that this 12.7 per cent became positive as a result of spontaneously acquired infection, and that a like number of the vaccinated might also have become positive for the same reason. But the difference between the figures for the two groups, 93.3 as compared with 12.7, is so great as to indicate clearly that artificial tuberculous infection in man, just as in the guinea pig, sensitizes to tuberculin.

The failure of 6.7 per cent to react is still to be explained. Several possibilities exist. In the first place it should be noted that the artificial infection, with the small doses of the nonvirulent BCG, rarely led to strong sensitivity. The reactions in the 12.7 per cent presumably spontaneously infected with virulent organisms were much stronger. It would not be surprising if, in a small number of the children, sensitivity from artificial infection did not reach a level sufficiently high for detection. However, another possibility must be considered, as will be made clear later, namely, that sensitivity may have been acquired and subsequently, within the year, lost. In any event the fact remains that after very mild infection an overwhelming majority of children became tuberculin-positive.

THE STANDARD PROCEDURE IN TUBERCULIN TESTING OF MAN

Reference was made in a previous paragraph to the occasional extraordinary tuberculin sensitivity in man. Because a few people react so strongly as to render testing with strong doses of tuberculin even dangerous, it is customary to use a two dose method, beginning with a small dose strong enough to detect the most sensitive reactors but weak enough to do so without danger, and proceeding with a much stronger dose in those failing to react to the first injection. In each case examination for reaction is made after forty-eight hours. A program carried out under this standard procedure thus requires four days, and a good deal of objection has been made because of the time required. Many engaged in large programs have compromised with the standard procedure by adopting an intermediate dose, on the one hand causing a few bad reactions, but not as bad as that which would have resulted from the final dose alone, and, on the other, frankly missing a few reactors of low allergy who would react to the customary final dose.

At present we are not concerned with the total number of tuberculin

reactors that may be detected, but rather with the detection of significant tuberculosis by the use of the tuberculin reaction as a preliminary screen. At this point it is essential that we agree on a definition of "significant tuberculosis" or the commoner equivalent a "case of tuberculosis." Probably the majority of us would not take exception to the definition adopted by a coöperating committee of the American Public Health Association and the National Tuberculosis Association, in which the term "case of tuberculosis" is restricted to infection with the tubercle bacillus which has proceeded to the point where it has produced symptoms recognized as those of clinical tuberculosis or has brought about changes demonstrated by X-ray examination that are considered by competent diagnosticians to indicate tuberculous disease. The definition is meant to cover pulmonary lesions of the well recognized active primary and active reinfection types of tuberculosis.

Thus, heavy responsibility is placed on X-ray examination, and it is now universally agreed that the latter procedure is our strongest weapon in tuberculosis case-finding. If the tuberculin test is used at all in case-finding, it is as a screen to obviate the necessity of the more expensive X-ray examination. Obviously the tuberculin test itself is not without cost in time and material expenses. The committee to which I have just referred has concluded that, on the basis of cost alone, it is not profitable to use the tuberculin test as a preliminary screen in groups where there is evidence that two-thirds or more of the group are positive. Saving X-ray examination of one-third of the subjects would not counterbalance the cost of the tuberculin test.

THE EFFICIENCY OF THE TUBERCULIN TEST IN CASE-FINDING

The question of present issue is the efficiency of the tuberculin test in singling out for X-ray examination all cases of tuberculous infection that have proceeded to the point where they are clinically significant, as the term has been defined above. For simplicity I shall restrict my remarks to the standard two dose testing procedure, not entering upon the question of an intermediate dose, which is of significance for later study and report only if the value of the tuberculin test by the standard method is fully established. In brief we may inquire what the standard first and second doses detect and overlook.

For this purpose I shall again quote the results of studies of colleagues at the Henry Phipps Institute, which will be reported in detail later, and which perhaps may be regarded as fairly well representative of results to be secured in large city clinics. Doctors Israel and Payne in reviewing

the history of five consecutive years in the clinic of the Henry Phipps Institute found that 610 cases of pulmonary tuberculosis were diagnosed. Of these, all but one reacted to tuberculin, and the overwhelming majority to the standard first dose of either the OT, used in the earlier, or the PPD used in the later years. In the one case in which reaction to the second dose failed to occur, the test could not be repeated. Among the 609 reactors it is noteworthy that 94 per cent of the white and 96 per cent of the colored patients reacted to the first dose. Attention has already been drawn to the somewhat higher sensitivity of Negroes.

It is thus evident that the vast majority of tuberculous patients in this particular clinic were tuberculin-positive. However, in other similar clinics and in hospitals attention is drawn occasionally to cases of unquestioned tuberculosis, even with positive sputum, in which the reaction is negative. Several explanations may apply. It is, of course, well known that patients in the moribund state, or the victims of overwhelming and rapidly progressive tuberculosis, may not react to tuberculin. It is known also that complications, both nontuberculous, such as acute pyogenic infections, and tuberculous, such as pleurisy with effusion, may abolish or greatly weaken the reaction. Additional explanations are possible, but cases of anergy in typical hospital patients, other than those falling into these categories, are probably few.

It may well be objected, however, that clinic experience is far from representative of the conditions of case-finding as they occur in mass surveys, that is, the subject of present discussion. These conditions themselves are very variable, for some surveys deal with groups of high infection incidence, and others with groups where the number of subjects infected is very low. From the many surveys now on record evidence is accumulating to show that the tuberculin test is an efficient preliminary case-finding measure in groups under relatively heavy exposure, as nurses in a general hospital or a tuberculosis sanatorium. Again, with the permission of two colleagues, I may quote the experience of the staff of the Henry Phipps Institute. Doctors Hetherington and Israel are at present engaged in a program of periodic tuberculin tests and X-ray examinations of a group of nurses in a large neighboring general hospital. The details will be reported later. Up to the time of writing, among 400 nurses on whom tuberculin tests were made at entrance on service, 22 "cases" of tuberculosis have occurred, all of which developed or already exhibited tuberculin sensitivity some months in advance of the onset of a recognized lesion. No case has developed in the absence of tuberculin sensitivity.

I believe the experience just cited represents fairly well the numerous studies of this character recently conducted. There seems to be general agreement that the tuberculin test is valuable as a means of detecting the occurrence of infection in groups under exceptional exposure, and as an effective warning sign indicating the need of close and frequent observation.

However, it must be admitted that such surveys are still not representative of the larger problem of case-finding. Unfortunately it is a fact that relatively few large surveys have been placed on record in which every effort has been made to study the efficiency of the tuberculin test as a case-finding mechanism in large groups not known to be subject to any special hazard. The now well known studies conducted by the United States Public Health Service in Alabama, Tennessee and Maryland, and the investigations of the Department of Health of the state of Tennessee, have been among the most important in this respect, and, as already noted, have furnished the impetus for the present extended consideration of the value of the tuberculin test in case-finding.

It seems clear from these studies that the tuberculin test is far from being the sharp indicator once popularly supposed of previous simple tuberculous infection. The investigations have brought to light a large amount of what appears to be healed primary tuberculosis in people not reacting to tuberculin. The implications for true case-finding have not been so clear, however, and for that reason supplementary tests under the auspices of the Public Health Service have been initiated.

The first of these, of which the detailed report is yet to be issued, was conducted at Hagerstown, Maryland, in the fall of 1938. A survey was organized for the triple purpose of comparing market tuberculins, studying the correlation of reaction and calcified lesions and investigating the tuberculin test as a case-finding procedure.

With the first two of these we are not concerned at the moment, and simply may note that the study confirmed previous results indicating discrepancy between tuberculins and the very frequent failure of reaction in the presence of calcified lesions. For case-finding purposes, however, tuberculin proved highly effective. In the one thousand subjects examined by both tuberculin test and X-ray, thirteen cases of tuberculosis, falling within the terms of the definition given above, were discovered. All but one of these reacted to tuberculin, and the various tuberculins used, although apparently of uneven strength, were all effective in this case-finding respect. The one case missed was of scarred apical disease, of slight extent and apparently long arrested. It was agreed by all

taking part in the survey to be on the border line of the cases to be considered "significant." All cases of what appeared to be active tuberculosis were positive to all tuberculins.

Naturally we must be cautious in making wide application of the results of a single survey. However, many considerations, upon which I shall not take the time to enlarge, lead me to believe that the results of the Hagerstown conference represent fairly well the conditions likely to be encountered in routine surveys. Recognizing that conditions will vary somewhat from place to place, I am inclined to believe that an accuracy on the order of 90 to 95 per cent may be expected of the tuberculin test as a means of selecting subjects for examination by X-ray. I will freely admit that a loss of 5 to 10 per cent is serious, however. A certain loss is, however, inevitable, as I shall try to show in the balance of this paper.

LIMITATIONS OF THE TUBERCULIN TEST

Probably most of the present confusion over the value of the tuberculin test arises from the popular conception of mankind as divided into two classes, namely, those who are infected and react to tuberculin, and those who are not infected and do not react. Unfortunately this simple separation can never be achieved, for reasons I shall now try to indicate.

In addition to those who have never been infected and are negative, and those who have been infected and are positive, it is necessary to recognize at least two other important groups, namely:

1: Those infected, not yet positive, but to be positive shortly thereafter, and
2: Those infected and previously positive, but now negative.

It is possible that a fifth group should be recognized, namely, those who are infected and never develop a positive reaction. This group is hypothetical, for without continued testing from the onset of infection we can never be sure that a transient allergy did not develop. We must remember, too, that our standards for the detection of allergy are arbitrary, and a hypersensitiveness too slight for detection by our methods may develop from very mild infection. Although some may feel that I am not giving sufficient attention to this possibly existent group, I shall devote my time to the two other problem groups, which I believe to be more significant.

To appreciate the importance of the first of these we need only recall that allergy does not develop simultaneously with infection. An animal infected with tubercle bacilli does not become positive to tuberculin for

several days or weeks. Presumably the same is true of man. If a thousand previously uninfected and tuberculin-negative children were infected to-day and tuberculin tested tomorrow, the entire thousand presumably would still be negative, although all would be infected. Yet, as we know from the extensive BCG experience to which I have referred, practically all of these children would become positive in the course of time. The period varies roughly from two or three weeks to the same number of months.

Obviously no such conditions will ever be met in mass surveys, but it is well to keep the fact in mind that in any large survey a few cases may be present in which infection has occurred and allergy has not yet developed. In some of these, in turn, lesions which can be seen in the X-ray film may develop, resulting in the record of a negative reaction and a positive film. Such cases have occurred occasionally in the dispensary practice of the Henry Phipps Institute. In every case that I can recall the patient, on retest, gave a positive reaction.

The second group, however, is more important. Indeed, in my opinion, it is the greatest single cause for our present confusion. Although it has been recorded repeatedly in the past, most of us have tended to overlook the fact that with the arrest and healing of tuberculous lesions allergy wanes and finally may disappear.

In days when infection was so wide-spread that a majority of the population were infected repeatedly throughout life, it was not to be expected that disappearance of allergy would be a conspicuous or frequent phenomenon. In a period, however, when the mortality rate is dropping steadily, and the morbidity rate is following in some proportionate relationship, and when in addition an improved control of tuberculosis is bringing about a steadily increasing isolation of patients with open lesions, it is only to be expected that reinfection, the rule in the past, will become progressively less frequent. The infections that formerly constantly restored a waning allergy will be far less frequent in the future and, I believe, we may look forward to the time when loss of allergy will be as common as its maintenance.

A graphic picture of the phenomenon of waning allergy can be given from the experience of approximately the last decade in the Henry Phipps Institute. The figures are presented through the kindness of Dr. Arthur Dahlstrom, assigned to the Institute by the United States Indian Service, who has studied the problem from numerous angles and will report his investigation in detail later.

Doctor Dahlstrom studied the records of 514 families on the Institute

rolls, with a total of 3,919 members. Of this large group 3,290 people, or approximately 84 per cent, were examined. The incidence of tuberculosis was high, namely, 913 cases, of all grades of severity, or 28 per cent. Of the group of 3,290, 2,490, or 76 per cent, were positive to tuberculin on the first or a subsequent examination. Of this total group of 2,490, 276, or approximately 11 per cent, became negative, either transiently or for the balance of the period of observation.

It is noteworthy that the disappearance of allergy could be closely correlated with its initial intensity and with the degree of household exposure. Table 1 shows clearly that the stronger the original reaction the less frequently it reverted to negative, and vice versa. In only 5

TABLE 1

Disappearance of allergy correlated with strength of original tuberculin reaction (Dahlstrom)

TOTAL NUMBER ORIGINALLY POSITIVE: 2,490		TOTAL NUMBER BECOMING NEGATIVE: 276
Positive reactors at each reaction level		Previous reactors becoming negative
First strength test	Number	Number according to previous reaction level
4 plus	28	1 (3.6%)
3 plus	1,090	4 (0.4%)
2 plus	692	13 (1.9%)
1 plus	320	41 (12.8%)
Second strength test		
3 plus	66	18 (27.2%)
2 plus	109	68 (62.4%)
1 plus	185	131 (71.9%)

out of 1,118 cases did allergy disappear in patients originally giving a three- or four-plus reaction to the first of the standard doses of tuberculin, while in 131 out of 185, or approximately two-thirds of the cases giving a one-plus reaction to the second strength of tuberculin, the reaction eventually became negative.

The correlation with exposure was equally striking. Doctor Dahlstrom divided the families, with respect to tuberculous exposure in the family group, as indicated in table 2. In the table the families are arranged in what is believed to represent a decreasing order of exposure. In 58 per cent of the families in which no tuberculosis was present when family care began, the tuberculin reaction became negative in some mem-

ber of the family. Approximately a fifth (21 per cent) of the once positive members of these families became negative to tuberculin. At the end of the table we see that reversion to negative reaction was rare in families in which a patient with sputum-positive tuberculosis resided continuously in the household. In only 8 per cent of these families, and only 1.5 per cent of the individuals concerned, did reversion to negative occur. Intermediate figures were found in the families with intermediate exposure.

The fact that allergy tends to disappear where there is no exposure, and has more and more tendency to remain as exposure is presumably more frequent, suggests strongly that reinfection is responsible for the main-

TABLE 2

Disappearance of allergy correlated with degree of household exposure (Dahlstrom)

	FAMILY GROUP*				
	A	B	C	D	E
Percentage disappearance by families	58	37	36	18	8
Percentage disappearance by individuals	21	12	9	3	1.5

* A: no tuberculosis in household when family care began.

B: sputum-negative tuberculosis in household when family care began.

C: sputum-positive tuberculosis in household when family care began, becoming sputum-negative.

D: sputum-positive tuberculosis in household when family care began, but contact terminated by death of patient or departure from family.

E: sputum-positive tuberculosis in family continuously.

tenance of the positive reaction. The epidemiological significance of this fact is obvious.

Table 3 correlates the disappearance of allergy with the results of chest X-ray examination of the patients concerned. In the 276 cases in which the reaction became negative, no abnormality was detected in the film in 258, or 94 per cent. There were no cases of active reinfection type tuberculosis in the entire group. In a few cases of scarred latent apical and in two cases recorded during the period of observation as active childhood type tuberculosis, the reaction became negative.

Especially noteworthy for present day discussion is the fact that in 10 cases with what were read as calcified lesions the reaction became negative. In the entire group of 3,290 patients examined calcified lesions were recorded in 577 people. In 25 of these cases the reaction to tuberculin was negative at the first observation. Since 10 more

patients with calcified lesions became negative after observation began, the tuberculin-negative state was noted in the case of 35, or approximately 6 per cent of all the patients with calcified lesions.

REINFECTION IN CASES IN WHICH ALLERGY DISAPPEARED

A question that may be expected to engage increasing attention in the future is the response to reinfection in patients with healed lesions, in whom allergy has disappeared. There will not be space here for extended consideration of this problem, but I shall cite two cases from the experience of Dr. J. D. Aronson in the United States Indian Service.

TABLE 3

Disappearance of allergy correlated with chest X-ray film (Dahlstrom)

ORIGINAL TUBERCULIN REACTION	X-RAY FILM				
		Tuberculosis Diagnosed			
First strength test	Negative	Active reinfection	Scarred latent apical	Active childhood	Calcified childhood
4 plus	1	0	0	0	0
3 plus	3	0	1	0	0
2 plus	13	0	0	0	0
1 plus	36	0	1	0	4
Second strength test					
3 plus	16	0	2	0	0
2 plus	66	0	1	1	0
1 plus	123	0	1	1	6
Totals.....	258	0	6	2	10

In the first of these, that of a girl sixteen years old at the beginning of observation, the tuberculin reaction was found to be negative to the strong dose of tuberculin on three successive occasions between December, 1935 and April, 1939. Films taken in May, 1936, February, 1937 and January, 1938 showed a well defined calcified nodule, but no other lesion. Late in 1938 the girl developed a minimal apical tuberculous lesion followed by a massive tuberculous pleurisy. The next tuberculin test, which was not made until March, 1939, resulted in a positive reaction to the first dose of PPD.

The other case was that of a girl fourteen years old at the beginning of observation, who was negative to both doses of tuberculin in January, 1936 and March, 1937, but became strongly positive to the first dose in

March, 1938 and was still positive in March, 1939. In films taken in April, 1936 and January, 1937 a calcified nodule was seen, but no other abnormality. In January, 1938, however, an infiltration in the right midlung field, with great widening of the mediastinum, was observed in the X-ray film. This was still present in January, 1939. As noted, the routine tuberculin test became positive at approximately the same time as the routine film.

In these 2 cases we have apparent examples of healed tuberculosis without allergy to tuberculin, in which reinfection sufficient to cause clinical disease developed, with establishment—presumably reëstablishment—of a positive reaction. It is notable that in one case the lesion of new infection had the characteristics of "reinfection type" and in the other of "primary infection type" tuberculosis.

Obviously one would not attempt to draw sweeping conclusions as to the resultant type of tuberculosis following reinfection in so few cases, but it is interesting to see a demonstration of what would presumably be classed as a second "primary infection." For present purposes the significant fact is that, with the development of the new infection, the tuberculin reaction became positive.

SUMMARY

Recently reported experience has prompted much discussion of the tuberculin test, and made desirable a revaluation of the test with indication of its limitations.

Discussion is here restricted to its use as a case-finding procedure, and the word "case" in turn is employed to designate only those instances in which tuberculous infection has progressed to the point where symptoms, signs or X-ray evidence of clinically significant tuberculosis have developed.

The conditions of human observation make the determination of the specificity and adequacy of the tuberculin test more difficult in man than in animals. The experience of BCG vaccination, however, has shown that in the overwhelming majority of human beings, artificial infection brings about tuberculin sensitivity, just as it does in laboratory guinea pigs. Sanatorium and hospital experience also indicates that a still more overwhelming majority of patients obviously suffering from pulmonary tuberculosis react positively to tuberculin.

Occasionally cases are encountered, however, in which evidence of tuberculosis exists, but the tuberculin reaction is negative. At present

we have only rough indications of how frequently this occurs. The few surveys made in which both tuberculin testing and X-ray examination have been carried out suggest that in ordinary practice the intracutaneous test with reliable samples of Old Tuberculin or Purified Protein Derivative tuberculin will detect 90 to 95 per cent of cases of tuberculosis.

The loss of 5 to 10 per cent of cases is attributable in large part to the variable conditions of tuberculin allergy. In any large survey, particularly of children, a few cases are likely to be found in which infection has occurred but the reaction has not yet become positive. Subsequent films in such cases may show lesions. Subsequent retest with tuberculin yields a positive result in such cases, but often the retest is not made.

A more important reason for the failure of the tuberculin test to detect all tuberculosis is the waning and disappearance of allergy that occur with healing. In this country of dropping tuberculosis morbidity and increasing isolation of patients with open tuberculosis this is probably a phenomenon of increasing frequency. It is apparently true that unless allergy is stimulated from time to time by reinfection, in cases of progressive healing of an existing infection, the intensity of response will diminish. In a large experience, of which a preliminary report is here given, 11 per cent of 2,490 patients passed in the period of a decade from the tuberculin-positive to the tuberculin-negative state. The tendency to become negative was directly and closely correlated with the intensity of the original reaction and the degree of continuing exposure. In this large series of cases there were no instances in which the reaction became negative in frank cases of reinfection type pulmonary tuberculosis, but there were a few examples of cessation of reacting power in patients with old scarred latent apical or childhood type tuberculosis. Conversion to the negative state was fairly frequent in cases with nodules interpreted as calcified lesions of primary tuberculosis.

Two cases are recorded in which tuberculin-negative children with calcified lesions became tuberculin-positive coincidently with the development of fresh, active tuberculosis.

X-RAY FINDINGS IN TUBERCULIN REACTORS AND NONREACTORS[1]

BRUCE H. DOUGLAS[2]

That tuberculin testing and X-ray examination of the chest of the reactor can be used as a method for surveying large numbers of persons for the detection of significant cases of tuberculosis has been widely demonstrated in this country and elsewhere. That this method is subject to certain errors has long been known. Just now, however, a careful appraisal as to the nature and extent of these errors is under way in many places. The final conclusions cannot as yet be drawn, but out of these studies there should come an even better understanding of the problem of detecting tuberculosis and better methods for the recognition of this disease in its earliest significant forms.

There has developed a certain confusion as to objectives in conducting surveys with tuberculin and X-ray examination and perhaps these should be redefined so that we may see just what it is we really desire to do.

1: There is the possible objective of measuring the extent of infection with the tubercle bacillus in a given community because of its epidemiological significance.
2: Again there is the objective of finding all those individuals who may have demonstrable X-ray evidence of primary tuberculosis, obsolete or otherwise.
3: It is conceivable that it may be thought desirable in a survey to detect all the possible pulmonary abnormalities of other types than just tuberculosis.
4: Finally, however, there is the objective of uncovering the significant active lesions of tuberculosis, either primary or reinfection type, which may be important to the health of the individual harboring them and of actual or potential import to the community because these individuals may be or may become sources of infection to others.

There may be other possible objectives, but those mentioned will probably cover most of the field.

When Chadwick (1) and his associates undertook the problem of deter-

[1] Presented at a Symposium on *Mass Tuberculin Testing and X-raying* at the 35th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, June 29, 1939.

[2] Detroit Department of Health, Detroit, Michigan.

mining the prevalence of tuberculosis among school children in Massachusetts some years ago, they sought a simple and yet as accurate a method as possible for examining large numbers. Their experience had shown that physical examinations of the usual type were of little value; that selecting underweight children for special study missed many; and that while X-ray films of the chest would find most of those with significant lesions still it was too expensive to apply to everyone, and alone was subject to certain errors of interpretation. Using tuberculin testing then as a screen to select from the many those who were infected with tubercle bacilli, and then carefully examining these including an X-ray film of the chest, was found to be a reasonably accurate method for the detection of tuberculous lesions. Myers (2, 3) in Minnesota and others used similar methods relying largely on tuberculin to select the infected individuals, basing their position on the experience in experimental animals and especially the experience of the veterinarians in detecting tuberculosis in cattle.

That these earlier workers recognized that not all those who showed evidence of possible primary tuberculosis reacted to tuberculin is shown in their own reports as well as those of many others. More recently there have appeared reports by Lumsden (4), Gass (5), and McKneely (6) among others who are inclined to believe, particularly in the case of Lumsden, that this failure of tuberculin tests and X-ray findings to correlate, vitiates the use of the tuberculin test as a procedure of merit in mass surveys. The points raised relative to the variations in different tuberculins are well taken. Whether the X-ray examination is to be accepted as as definite a detector of tuberculous infection as these workers would suggest may be open to question.

That various interpretations have been put upon the significance of the reaction to tuberculin and the finding of certain calcified lesions and other X-ray evidences of scars in the lungs should not detract from the fact that, after all, there is little evidence to indicate that persons with really active tuberculous lesions of either primary or reinfection type fail to react to tuberculin, except in well known circumstances, such as during certain acute communicable diseases, terminal states of or very acute forms of tuberculosis itself, the later weeks of pregnancy and following certain severe surgical operations, to mention some of the more important conditions that may result sometimes in loss of sensitivity.

From a practical standpoint the greatest concern it would seem should

be with the fourth of the objectives listed, namely, the finding of the clinically significant active tuberculous lesion of either primary or reinfection type.

Since tuberculosis is a communicable disease, and since the chief sources of infection are cases with active tuberculosis, if these can be discovered in goodly proportion, isolated and treated, there is every reason to believe that this disease can be still further limited by checking the spread of the tubercle bacillus.

While there may be some question as to the significance of an obsolete primary infection as demonstrated by a positive tuberculin test or a presumably healed primary lesion as seen in the X-ray film, there is no debate in anyone's mind as to the importance of discovering the active case of tuberculosis, particularly the reinfection or adult type, as of prime importance in the control of this plague.

It is important then to be able to discover from among the many those who have active tuberculous lesions.

Medicine has never been an exact science and while the science of diagnosis has reached a high point of efficiency in detecting many diseases still practically every diagnostic procedure now employed is subject to certain errors growing out of exceptional conditions in which the test or other procedure fails to respond in the expected manner.

We are indebted to the late Lawrason Brown (7) and his associates for pointing out to us the relative merits of certain diagnostic procedures when applied to the diagnosis of pulmonary tuberculosis. His five criteria do not include tuberculin testing. But of the five, history of pleurisy, of haemoptysis, the finding of râles in the upper third of the lung or lungs, the typical lesion in the roentgenogram and tubercle bacilli in the sputum, the X-ray findings were definite in 96 per cent of the cases, being by far the most helpful single criterion in making a diagnosis.

However, this method contemplates the making of a diagnosis as accurately as is possible in the individual presenting as a diagnostic problem, whereas in case-finding the effort is directed toward finding as nearly as possible all the significant cases of tuberculosis in a large number of individuals, most of whom are presumably well.

The problem then is to narrow the field as quickly and economically as possible and yet without a gross error. Tuberculin testing has been useful in doing this very thing particularly in communities where the reactor rate is low.

It remains, however, that an X-ray examination of the chest is the best means available for examining the reactors for the presence of significant lesions in the lungs.

Why not then examine everyone by means of the X-ray when examining large numbers? Of course this has been done extensively and quite successfully, but up to the present, at least, the cost of making roentgenograms has made this too expensive for universal use.

Several methods have been used to lessen the cost factor and make possible extensive mass X-raying. To list some of these:

(*1*) Fluoroscopic examination instead of the film exposure has been used and, even though it requires an experienced operator to make such an examination, it can be done quite reasonably but does have the disadvantage of not being as accurate as the well taken film and it furnishes no permanent record.

Fellows (8), McCain (9), and Bloch (10), to mention a few, have found this method very useful and reasonably accurate in examining large numbers for evidence of pulmonary disease.

A recent practical demonstration of this method occurred in Texas where the Michigan State Health Department (11), the United States Public Health Service, and the Michigan Sugar Beet Growers Association coöperated in examining over 4,000 Mexican laborers before taking them to Michigan for summer work. Part of the examination consisted of a fluoroscopic examination of the chest with the newest type of portable fluoroscope. As a result of this study, 81 cases of pulmonary tuberculosis were found and excluded from being transported for work and were of course reported to the local health authorities.

(*2*) Sensitized paper has had quite extensive use, having been used most widely in mass surveys by Edwards (12) in New York where it has proved valuable. It has been noted by Edwards and others that sensitized paper should be freshly made and kept in cold storage if necessary to keep for any length of time before using if the best results are to be had. There have been marked improvements in this material in recent years. While cheaper than regular film, it is still expensive enough to consider tuberculin screening in groups where the reactor rate is low. For mass surveys of adults this material can be used economically.

(*3*) Some attention has been given to saving on film costs by using a 14 x 14 film instead of the usual 14 x 17 size and this has been found to result in a 20 per cent saving in film cost as reported by the staff of the Middlesex County Sanatorium (13) in Massachusetts.

(*4*) Considerable experimentation is under way in the making of miniature chest films by photographing the fluoroscopic image on small size films. Holm (14) and his associates in Copenhagen, Dormer and Collender (25) in England and workers in South America and Germany have made such pictures on 35 mm. film and then enlarged them on a screen or by printing and believe this to be an inexpensive and practical method of making mass surveys. Potter (15) working with the General Electric X-ray Corporation has developed a special screen and camera that will produce a miniature chest image on a 4 x 5 inch film which is large enough for direct reading and offers great promise of making mass surveys simple, economical and accurate. This is still in the experimental stage, but is now being given a clinical trial in Detroit.

In using the X-ray examination there are, however, definite limitations and some of those who have used the X-ray as a check as to the accuracy of tuberculin testing as an indication of infection with the tubercle bacillus have seemingly lost sight of this fact. Myers (3) has recently pointed out the twofold nature of these limitations which, on the one hand, cause obstruction to a complete view of the lung fields due to mediastinal and heart shadow, *et cetera*, and, on the other hand, are due to the many nontuberculous lesions that may be seen.

There is an impression abroad that a roentgenogram will reveal very definitely whether tuberculosis is present or not and that when it is present it is so simple that "he who runs may read." Such is not the case. Experience in interpretation is most important and the interpreter, who having found evidence of a lesion, will wish to support his opinion with other pertinent data, particularly sputum examination and tuberculin test.

With the X-ray examination, the element of error is present as in most diagnostic procedures, so that substituting the X-ray as the only mass examination instead of using tuberculin testing as a screen does not avoid all chance of missing cases.

For example, primary lesions are often elsewhere than in the clearly seen lung fields. Even reinfection lesions may be hidden.

In figures 1 and 2 we have an example of the distribution of calcified lesions as seen in the roentgenogram of the living patient with the postmortem X-ray examination of the removed lungs and lymph nodes, indicating what a large amount of calcium deposit was not in the usual field of vision.

Figures 3 and 4 illustrate the even more important possibility of missing

a definite reinfection type lesion. This patient following an acute communicable disease was at first thought to have basal bronchopneumonia. Certainly, the location and appearance of the lesions were not typical of tuberculosis. Sputum analysis, however, revealed tubercle bacilli and a film in the oblique position showed a definite cavity behind the right heart border. X-ray examination with a single film alone in this case could easily have resulted in a mistaken diagnosis.

There are, however, certain advantages in convenience to the public in ease of administration in using X-ray examinations directly without previous tuberculin testing inasmuch as it necessitates fewer visits by those to be examined. As a consequence, there is less loss growing out of failure to return for a reading of the test or failure to get an X-ray examination by the reactor. One visit to have an X-ray examination and a return for a report of the result will suffice except when something requiring further study is found. Even a failure to return for the report does not mean a loss of the case for the record is made and the patient may be followed up. Generally speaking it is easier to persuade people to have roentgenograms made than to have a scratch, a needle prick or even a patch on the arm.

There are certain situations where tuberculin testing is unusually advantageous. It has been found by some observers, Asserson (23), Brailey (24) and others for example, that in the examination of infants it is very useful. Here it is of course difficult to get uniformly good X-ray films of the chest and a positive tuberculin test is of definite significance not only for the child but as a possible lead back to the source case in the infant's family. In older children there is a difference of opinion in regard to following back into the family as a profitable method of finding source cases, but much of the experience tends to indicate that it is not productive.

Tuberculin testing is useful also as a diagnostic aid in those cases where a lesion has been found by X-ray examination in which the sputum is negative and the appearance atypical. If under these conditions no

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FIGS. 1 & 2. Comparison of antemortem roentgenogram with roentgenogram of lungs of same patient after removal at postmortem revealing much more evidence of calcification than was visible in the examination during life.

FIGS. 3 & 4. Roentgenogram in usual position is not suggestive of tuberculosis but patient's sputum is positive and an oblique position reveals a cavity at the base of the right lung previously hidden.

FIG. 5. Lesions seen in roentgenogram simulate tuberculosis yet tuberculin test was negative. There were no tubercle bacilli in the sputum and the organism *coccidioides imitis* was found.

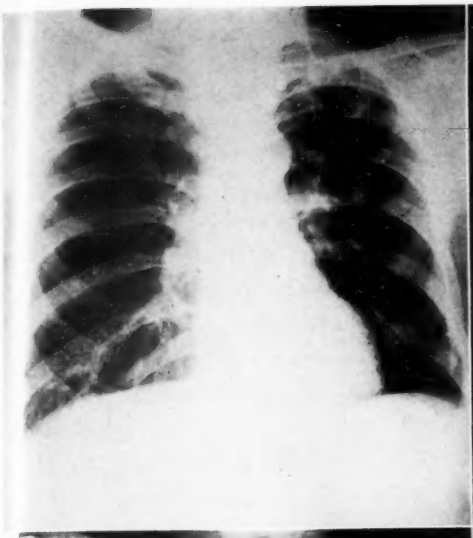

FIG. 1

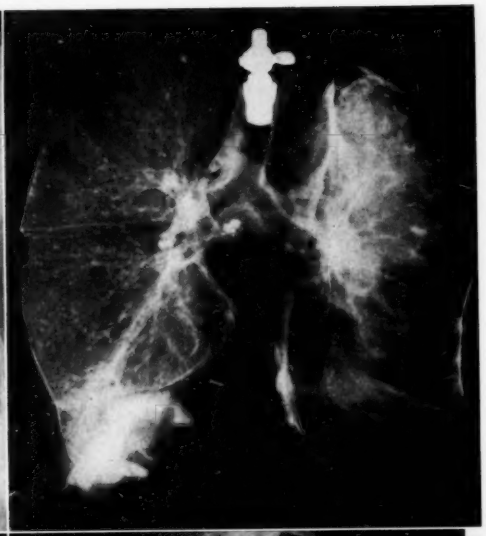

FIG. 2

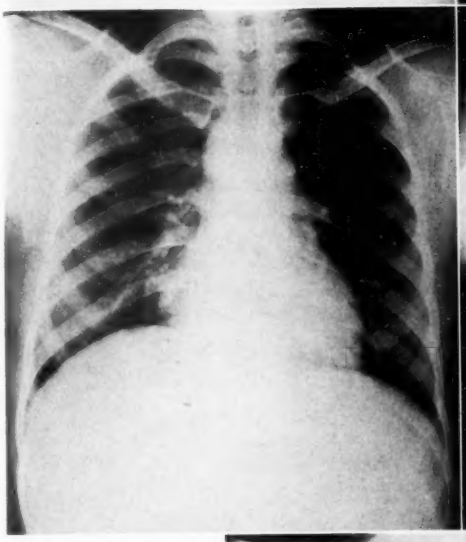

FIG. 3

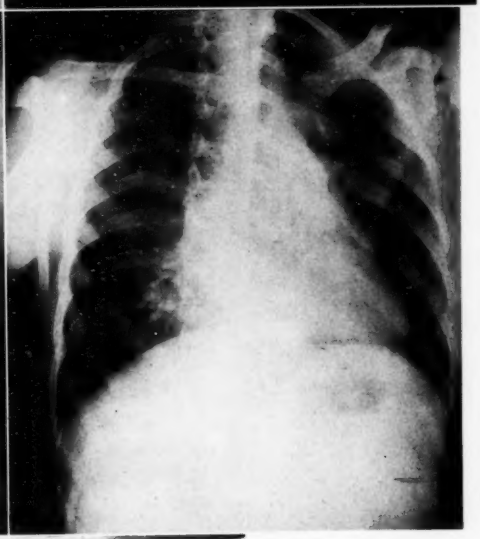

FIG. 4

FIG. 5

FIGS. 1–5

reaction to tuberculin is found it is very strong evidence against a diagnosis of tuberculosis.

A third case illustrated in figure 5 would from the X-ray appearance certainly be called tuberculosis. However, this sixteen year old boy failed to react to tuberculin and no tubercle bacilli could be found in the sputum. *Coccidioides imitis* was found, however. Here again the roentgenologist was dependent on further data, the chief clue to a non-tuberculous lesion being a failure to respond to tuberculin. This case is presented through the courtesy of Dr. Charles W. Mills (16) of Tucson.

The X-ray examination, however, can be credited with having discovered these lesions even though an exact diagnosis of their nature could not be made.

The question of diagnosing tuberculosis by X-ray examination in the absence of tubercle bacilli in the sputum is an important one. Unless the lesion is very typical and other possibilities pretty well excluded, the diagnosis of tuberculosis should not be made when tubercle bacilli cannot be found in the sputum.

Definite clinical tuberculosis rarely fails to respond to tuberculin. A study made at the Maybury Sanatorium (17) on the relation between tuberculin sensitivity and clinical course and reported in 1937 did not reveal a single case in which a patient with clinical tuberculosis, followed for from one to two years with repeated tests, was at any time negative to tuberculin (TPT) or OT. There was noticeable fluctuation in sensitivity during the period of observation which could not be related to changes in the clinical course of the disease.

Recently Mussachio (18), an associate of the author, has tested 500 adult patients with X-ray and clinical evidence of tuberculosis and only 9 failed to respond to the usual doses, repeating with 10 mg. of OT brought only one more positive response. All of these nonreactors were terminal cases, except one which by X-ray appears to have a moderately advanced mixed type lesion with no cavitation and a sputum negative for tubercle bacilli. This may be a pneumonitis of some other type but as yet it has not been determined. Granted this case is tuberculous, it represents an unexplained error of only 0.2 per cent.

Results in testing 500 clinical cases of tuberculosis

	Positive	*Negative*
Minimal pulmonary tuberculosis	25	0
Moderately advanced pulmonary tuberculosis	157	1
Far advanced pulmonary tuberculosis	274	6
Other forms of tuberculosis	36	1
Totals	492	8

Condition of 8 nonreactors with clinical and X-ray evidence of tuberculosis

Far advanced pulmonary tuberculosis in or near terminal state, sputum positive	6
Moderately advanced pulmonary tuberculosis but negative sputum	1
Bilateral renal tuberculosis near terminal state	1
Total	8

The question may arise as to whether these patients had been previously tested as a basis for the original diagnosis. This was not the case except in a few instances, practically all of these having been diagnosed on the basis of symptoms, X-ray examination and sputum studies.

In mass surveys, however, it is not necessary to apply immediately all the refined diagnostic methods. The problem concerns itself with selecting for more careful study a relatively small number of persons from a large population of presumably well persons.

Experience with tuberculin testing by a large number of physicians with X-ray examination of the reactors as carried out in Detroit (19, 20) reveals some interesting points in connection with the selection of the reactors by this method. While there is no control group in which all were X-rayed as well as tuberculin tested, still it is interesting to note the proportion of cases found by this method as shown in the following table.

Tuberculosis Case-Finding—Detroit

Distribution of tuberculin tests and cases of clinical tuberculosis according to age of individuals tested

April 16, 1937—January 1, 1939

AGE	TUBERCULIN TESTS REPORTED			CASES OF CLINICAL TUBERCULOSIS	CASES OF CLINICAL TUBERCULOSIS PER 1,000 TUBERCULIN TESTS	CASES OF CLINICAL TUBERCULOSIS PER 1,000 POSITIVE TUBERCULIN TESTS
	Total	Positive	Per cent Positive			
years						
0–9	22,798	1,384	6.1	28	1.23	20.23
10–19	25,035	4,665	18.6	108	4.31	23.15
20–29	23,290	8,874	38.1	208	8.93	23.44
30 & over	37,315	16,590	44.5	292	7.83	17.60
Age not stated	279	79	28.3	2	7.17	25.32
Total	108,717	31,592	29.1	638	5.87	20.19

As is well known, the percentage of reactors will be noted to have increased with age and the younger age groups do not yield as many significant cases as are found among the adults, the percentage reacting being only 6.1 per cent from 0–9 years and only 1.23 cases per 1,000

tested at this age. At 20–29 years the reactors are over six times as frequent or a percentage of 38.1, and the significant cases were over seven times more frequent than in the younger group, or 8.93 per 1,000 tested.

However, it is very striking that regardless of age, once the reactors are selected, the number of cases found per thousand reactors is nearly the same in all age groups, this being about 20 per 1000 or 2 per cent.

While there should be a large group of nonreactors who were X-rayed to compare with this experience (which unfortunately there is not), still this observation suggests a very definite relationship between tuberculin reactors and persons having the disease.

It also demonstrates that even in a large city population the percentage of reactors is not as high as might be expected and that, granted an error may be present, it still has formed a basis for finding a goodly number of active cases of tuberculosis requiring isolation and treatment. Knies (21) has recently reported that the ideal way to select most of the infected persons in a group would be to employ both tuberculin testing and X-ray examination. In his study he relied principally on the fluoroscope for the X-ray examination and found that tuberculin testing failed to detect 26 per cent of the lesions which he interpreted as being due to infection with the tubercle bacillus, and that fluoroscopy failed in 9.7 per cent of the positive tuberculin tests. So by combining the methods, he believes the error would be minimized.

Many no doubt would not agree with Knies that fluoroscopy is an adequate method of X-ray examination nor would everyone agree on what represents X-ray evidence of infection with tubercle. But the point is well taken, since the evidence presented by Doctor Long (22) definitely indicates that many persons once positive to tuberculin become subsequently negative, that there would be a chance to uncover more complete evidence of present and past infection by combining the findings of X-raying the chests of the whole group and tuberculin testing them all.

This, however, does not seem a practical thing to do, except perhaps for study purposes, and if we return to the premise that it is the active lesion of tuberculosis that we are concerned with and since we rely to a large extent on the X-ray examination for diagnosis it would seem logical that for the detection of active lesions an adequate examination of all by X-ray will result in fewer missed cases than tuberculin testing and then X-raying the reactors.

Tuberculin can, however, be of distinct value in diagnosing the atypical pulmonary lesion with a sputum negative for tubercle bacilli.

In order that X-ray examinations be done on a wide scale as a mass case-finding method, it is necessary that a reasonably accurate method that can be economically carried out be employed. It is believed that the miniature film offers great promise for realization of this goal, though it is too early to be certain.

The ideal of taking a full size chest film on everyone is, under most circumstances, out of the question because of cost. There is, therefore, still a very valuable place for tuberculin as a preliminary screen in groups of relatively low reactor rate.

The group with high reactor rate, 50 per cent or more, can even now be examined by X-ray more satisfactorily than with a previous tuberculin screening. This is particularly true of industrial groups where time is a factor and where there is interest in discovering other lesions than just tuberculosis.

There is room for improvement in our technique in doing mass surveys. Tuberculin testing and X-ray examinations both have their shortcomings. Increased accuracy and ease of application are most desirable.

SUMMARY

1. In mass surveys the chief consideration should be the finding of the active cases of tuberculosis. The finding of evidence of inactive or obsolete lesions is of less importance.

2. The tuberculin test has long been known to be subject to certain errors due to anergic states that may develop under certain well known conditions, such as during certain acute infectious diseases and in terminal states of tuberculosis itself.

3. The X-ray examination has certain very definite limitations. Small lesions may be inaccessible and not seen. Its value is directly related to the experience and ability of the interpreter.

4. Granting the presence of error, tuberculin has been useful in screening from the many the few who should be further examined by the more expensive X-ray examination.

5. The tuberculin test is rarely negative in the presence of significant active tuberculosis: 8 out of 500 cases, 7 of whom were terminal.

6. As surveys are conducted and ignoring the cost of an X-ray film, examination of everyone in the group can be carried out with less incon-

venience to those examined and with less missed cases than by using a preliminary tuberculin screening.

7. There are several types of X-ray examination being used that seek to bring down the cost factor, fluoroscopy, sensitized paper and miniature films, all of some merit but none of them yet sufficiently developed to entirely supplant tuberculin testing on the basis of accuracy or economy.

8. There is every indication that one or more of these X-ray examination methods will be developed to an acceptable point and tuberculin will then be used as a diagnostic aid in such problems as the determination of infection in infants and very young children and in cases of atypical lesions in adults where tubercle bacilli cannot be found.

The final word cannot be said on this problem as yet but even though our tools are not perfect let us not be discouraged in using them, standing ready to adopt new and better ones when they shall have been thoroughly tested.

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THE TUBERCULIN TEST IN THE CONTROL OF TUBERCULOSIS[1,2]

JAMES A. DOULL

In his original communication announcing the discovery of the tubercle bacillus, Koch emphasized the prime importance of attacking sources of infection: "First of all, the sources from which the infectious material flows must be closed as far as this is humanly possible. One of these sources, and certainly the most essential one is the sputum of consumptives. . . ." (1)

Almost sixty years have since elapsed and, although great progress has been made in diagnosis and treatment and in education of the public, it may fairly be said that no more promising means of prevention has been discovered. No acceptable method of artificial immunization is yet available and no specific cure for the disease. The reduction of exposure, by early detection of the open or potentially open case, followed by prompt isolation, still offers the best hope for eventual eradication of the disease.

In assessing the probable usefulness of any control measure, therefore, the first criterion must be the extent to which it can contribute to this primary objective. Feasibility of application and cost are necessary considerations but only in making a choice of methods apparently of more or less equivalent value in reaching this objective.

The avowed purpose of the mass use of the tuberculin test to-day is usually in strict conformity with this criterion. Its extensive use as a "screen," chiefly on school children, is designed to detect, ultimately, those with active tuberculosis. And its application to the same group as a case-finding measure is based on the possibility of finding the sources from which tuberculin-positive children have been infected.

(1) Mass tuberculin testing as a screening measure: It is difficult to estimate the value of the tuberculin test in the diagnosis of active tuberculosis. A negative test excludes active tuberculosis with a high degree

[1] Presented at a Symposium on *Mass Tuberculin Testing and X-raying* at the 35th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, June 29, 1939.

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of probability. With the decline in tuberculosis the negative test may become a very significant item in diagnosis. The positive test has its chief value in infancy and, since the proportion of positives becomes higher with advancing age, the test becomes progressively less economical as a screening measure.

In the younger ages we have too little accurate data regarding the incidence of active tuberculosis. Assuming that the morbidity curve follows that of mortality, more or less, it is clear that at the ages when the "screening" might be most useful the incidence of active disease is at a low level as compared to the number of infections.

In the Philadelphia report of Hetherington, McPhedran, Landis and Opie (2), it is stated that the percentage of tuberculin-positives was 54.2 for children of from five to nine years, and 76.6 for those of from ten to fourteen years. Accepting the former figure for children of seven and one-half years and the latter for those of twelve and one-half, and making no allowance for regression from positive to negative, the average annual increment of tuberculin-positives between these ages is 4,500 per 100,000 children. Since it is improbable that the annual death rate from tuberculosis for children from seven to twelve years of age would exceed 15, the ratio of new infections to each annual death is, therefore, something above three hundred.

The Philadelphia report also gives some data on the number of active cases likely to be found among school children positive to the tuberculin test. Among 1,512 children of ten to nineteen years of age, reacting to tuberculin and examined by X-ray, 14 cases of "manifest tuberculosis" were discovered, a ratio of 108 to 1.

Without claiming that the specified ratios have general applicability, the following conclusion, nevertheless, appears obvious: At the ages when the tuberculin test is economical as a "screening" measure, the incidence of open tuberculosis is so low as to raise serious doubts as to its validity as an administrative procedure.

(*2*) *Tuberculin testing as a case-finding procedure:* The relatively high incidence of infection among household contacts has given impetus to the use of the tuberculin test as a case-finding measure, particularly in younger school children. Obviously, the value of the method will depend materially on the prevalence of infection in the general population. And since it can be of service only if previously unknown cases are discovered, its value will depend also on the completeness of notification in the area.

Any health officer who is using the tuberculin test on school children may make a rough calculation of the probable value of this method of case-finding. As a starting point, the number of active cases in the community is estimated, making this estimate as high as is at all likely, say, ten times the number of deaths occurring each year. From this figure there is subtracted the number of registered active cases. The remainder is multiplied by the average number of persons per family in the families of registered cases and this population is distributed according to the age constitution of these families. Applying to these age groups the corresponding percentages of tuberculin-positives usually found in household contacts, the approximate number of positives in the community who are living in such contact with unregistered cases may be obtained.

As an example, let us restrict the problem to children of a specified year of age. The total number in the general population may be termed P and the estimated number in household contact with unregistered cases, P^1. If 10 per cent of all children of this age, and 80 per cent of those of the same age living in household contact with a case of tuberculosis, give a positive reaction, the chance that a tuberculin-positive child belongs to a household of an unregistered case is $8\ P^1/P$; or expressed in a simpler way, this proportion of the families represented by all tuberculin-positive children would have to be examined, on the average, before a single unregistered active case would be found.

Actual data on the costs of different methods of case-finding are not numerous or at least are not readily available. In New Haven, it was found by Edwards and Unzicker (3) that the routine examination of family contacts to children with positive tuberculin reactions proved to be unreasonably expensive. The families in their series were divided into three groups: (*1*) primary case, pulmonary tuberculosis; (*2*) primary case, a child with a positive tuberculin reaction; and (*3*) primary case, tuberculous meningitis. The cost for each diagnosed case of pulmonary tuberculosis of the adult type, including nursing visits, dispensary service and X-ray films for each family group, was as follows: (*1*) $149.51; (*2*) $1,063.50; (*3*) $78.00.

The procedure of visiting and examining family contacts of tuberculin-positive school children is, nevertheless, widely practiced in American cities. On theoretical grounds, it would be a much more promising method if only those families were examined in which two or more positive children were found. No data of this type have come to the writer's attention.

(*3*) *As an index of the prevalence of active tuberculosis:* Almost since its introduction, the tuberculin test has been regarded as our most practical means of determining the extent of tuberculinization of a community. One of the earliest studies was that of Metchnikoff and his colleagues (4). In 1911, using the Pirquet test, these workers tested Kalmouks living in the steppes west of the Caspian Sea and south of the Volga. In the central and more isolated regions, 54 per cent of adults were found positive; whereas in Astrakhan and the more accessible villages the comparable proportion was 84 per cent.

In the past thirty years studies on this subject have become more refined and precise and the results are so generally known that an extensive review is unnecessary. It will suffice to state that a positive correlation has been established between the proportion of individuals of a given age who react to the tuberculin test and the incidence of open tuberculosis in the community of which they are members. The highest proportion, for example, is found among those in household contact with open cases; the proportion is higher in densely populated areas than in suburbs of our cities, and it is lowest in sparsely settled rural areas.

Although there is a general positive correlation, there is no reason to believe that it is necessarily extremely high. And it is probably quite unlikely that the percentage of tuberculin-positives in a community will decline proportionately with the death rate. In one of his last papers, the late Dr. W. H. Frost (5) touched upon this point. "It is also to be remembered that the frequency of exposure to the tubercle bacillus may have been reduced much more than would appear to be indicated by the results of tuberculin tests. For instance, if we find that at 15 years of age 60 per cent of the population show a positive tuberculin reaction, which we may take as evidence of prior infection with the tubercle bacillus, it is obvious that, under the worst conditions which can have existed in the past, the proportion infected before reaching this age could not have been greater than 100 per cent. It may therefore appear that there can have been no more than a 40 per cent reduction in the prevalence of infection, whereas we know that there has been a much greater reduction in mortality. However, assuming a random distribution of exposure, the rate which would result in infecting approximately 99 per cent within 15 years is some 4 times the rate which would infect only 60 per cent within that period."

Doctor Frost did not elaborate the point as he recognized clearly that some of the assumptions necessary to this calculation are improbable.

But if the distribution of infection in a community is at all random, and if susceptibility to infection is more or less universal, the fall in the infection rate may be far more rapid than would be indicated by the decline in the proportion of tuberculin-positives.

It is a significant fact that although there has been a tremendous decline in mortality from tuberculosis, there is evidence that the risk for household contacts has not been appreciably reduced. The data of Downes (6), for example, indicate approximately the same mortality rates for those exposed in household and born between the years 1868 to 1897 as for those exposed and born during the period 1904 to 1913. As the disease declines, therefore, it is apparently more and more concentrated in the immediate environment of the open case.

Surely, therefore, the field of action is becoming more sharply delimited. The population primarily at risk is, admittedly, not completely enumerated in any community. But a large proportion of these individuals are listed on health department records, being members of families of those who are known to have open tuberculosis or of those known to have died of the disease.

There is no place for diffuseness in the tuberculosis program. Nevertheless, time and money are being dissipated in many types of indirect effort. Only when a health department has isolated in sanitoria all its known open cases, when all active cases not in the open stage are under medical care, when a high proportion of all household contacts are undergoing periodic medical examination, including examination by X-rays, when a system of financial subsidy is arranged for needy dependents of wage earners who have been attacked—only then should any consideration be given to indirect methods not of established value, such as that under consideration to-day.

Nothing that has been said should be interpreted as discounting the need for further research on tuberculin and on the type of reaction which it induces in man and animals. On the contrary, there is urgent need for such research. The discussion here presented relates exclusively to the application of the tuberculin test to the administrative control of the disease.

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TUBERCULIN AND X-RAY SURVEY[1]

Observations in Giles County, Tennessee

W. PALMER DEARING[2]

I am particularly glad of the opportunity to participate in this discussion, since the work of the group with which I am associated has been misinterpreted as discrediting or attempting to discredit the use of the tuberculin test for any purpose whatsoever. This misunderstanding is the result of failure to distinguish between the clinical uses of tuberculin for case-finding and diagnostic work, and its epidemiological use for establishing and comparing infection rates or indices at different times and places. The report of Lumsden, Dearing and Brown in 1938 (1) called attention to the lack of uniformity among widely used and supposedly standardized tuberculin preparations, and to the lack of correlation between tuberculin findings and morbidity and mortality rates in two communities with widely different tuberculosis situations. Their report also confirmed the findings of Gass, *et al.* (2) that there was a high incidence of typical, roentgenologically demonstrable, apparently tuberculous calcification in the children of middle Tennessee, which occurred almost as frequently among tuberculin-negative as among tuberculin-positive reactors. It was evident that these findings cast doubt on the epidemiological value of the "tuberculin survey" for measuring the tuberculosis problem in a community or for comparing tuberculosis incidence at different times and places. The authors specifically pointed out, however, that the discrepancies did not necessarily invalidate the use of any of the tuberculins for case-finding and diagnostic work. Doctor Long has admirably summed up the present status of the problem in his editorial in the April number of the AMERICAN REVIEW OF TUBERCULOSIS.

The tuberculin test, however, is a technical procedure, carried out with variously prepared biological materials in varying dosages which give

[1] *Discussion* of papers presented at a Symposium on *Mass Tuberculin Testing and X-raying* at the 35th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, June 29, 1939.

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different results, rather than an ideally perfect, abstract entity. It is pertinent, therefore, to reëmphasize that the failure to standardize tuberculin preparations, the lack of uniformity of dosage, and the varying classifications of degree of reaction are still germaine to any consideration of this problem. Douglas, in using dosages up to 10 mg. of Old Tuberculin to bring out reactions in some of his cases goes beyond any procedure officially recommended for routine work, so that his results can hardly be applied to the problem of mass testing. Long and Douglas both state that the "tuberculin test" is an efficient and specific procedure for case-finding work, without specifying whether they refer to the three-dose Mantoux or the Pirquet test, both used by Douglas, to two-dose testing with Old Tuberculin or Purified Protein Derivative, or to single-dose testing with one of several preparations which gave in our hands incidences of reactors varying as much as several hundred per cent in the same individuals. Any discussion of the usefulness of the tuberculin test should specify at least the preparation and dosage under consideration; otherwise it lacks practical application.

It is my purpose to-day to discuss the tuberculin and X-ray findings among approximately 4,500 white residents of Giles County, Tennessee, examined by our traveling clinic between February and October, 1938. These examinations were done in the course of a study, still in progress, undertaken by the United States Public Health Service in 1936 (3), to determine the causes of the high mortality from tuberculosis in middle Tennessee and Kentucky as compared with the Coastal Plain to the south and east.

About 3,000 children and 1,500 adults were examined. Of the children, 2,200 constituted over 90 per cent of the population of nine twelve-grade schools and were otherwise unselected. The remaining subjects, constituting more than 10 per cent of the white population of the entire county, were self selected in that they voluntarily came to a scheduled clinic in their community for the examination.

Tuberculin tests were done by the Mantoux method with a single dose of 0.000,5 mg. (one-tenth of the official second strength dose) of PPD. Eighty-seven per cent of the tuberculin reactions were read in forty-eight hours and the remainder at seventy-two. There was no significant difference in incidence of reactions between the two groups.

X-rays were flat postero-anterior plates with a 15 milliampere portable X-ray unit at 40 inches. Films were all read by Dr. R. A. Brown without knowledge of the tuberculin reaction, history or other clinical in-

formation on the patient. It was recognized that this procedure is not definitive for clinical evaluation of many pathological shadows. Even with the patient at hand, repeated studies over a period of time may be necessary, and sometimes only the pathologist definitely establishes the diagnosis. The objectivity of this method, however, tends to produce greater uniformity in interpretation; the roentgenologist is not led by a history of family contact and a positive tuberculin reaction to attach

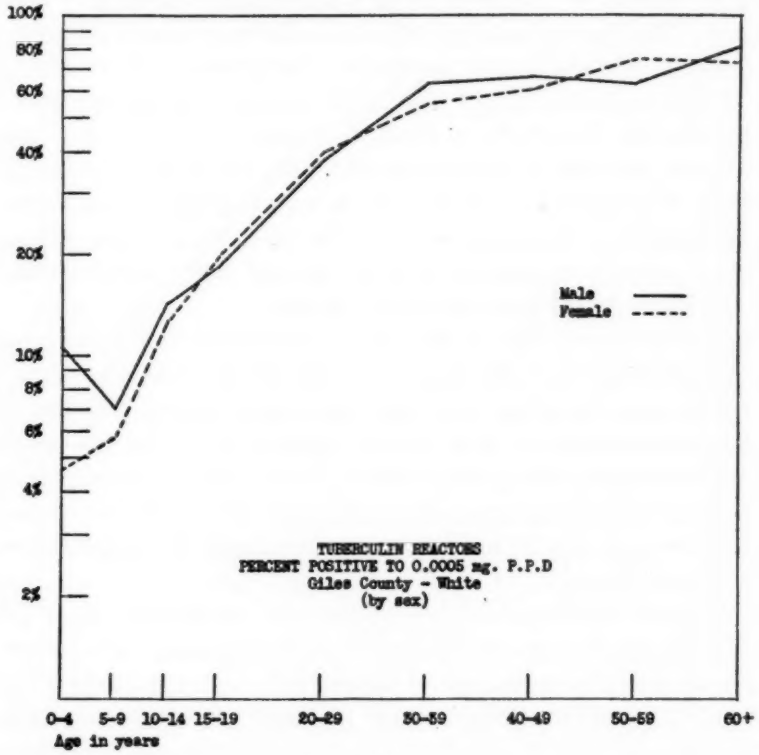

CHART 1

significance to faint shadows which he might disregard in an individual with negative history and tuberculin. Definite shadows, only, were described; where the shadows were typical in appearance and location, a diagnosis was made, recognizing its limitations. Where shadows were atypical, questionable or alternative diagnoses only were made. The procedure and its limitations were explained to the family physicians, and arrangements were made with the County Health Department and

the State Diagnostic Clinic to follow up these cases for classification and control. As follow-up examinations are made, our diagnoses are reconsidered in the light of the entire picture.

The incidence of tuberculin reactors by age and sex is shown on chart 1. Although the reaction rates in children are very low—well under 20 per cent at high school age—the rates rise to 70 per cent or more in old age. Gass in a neighboring county found much higher rates in children with Old Tuberculin, but the rates in old age were comparable with ours. Similar results were obtained in duplicate testing with PPD and Old

TABLE 1

Tuberculin reactions

Giles County—White

AGE	MALE			FEMALE		
	Total tested	Total positive		Total tested	Total positive	
		Number	Per cent		Number	Per cent
years						
0–4	76	8	10.5	65	3	4.6
5–9	469	33	7.0	471	27	5.7
10–14	564	80	14.2	683	87	12.7
15–19	333	61	18.3	412	80	19.4
20–29	192	73	38.0	268	106	39.6
30–39	146	91	62.3	187	102	54.5
40–49	99	66	66.7	153	93	60.8
50–59	75	47	62.7	86	64	74.4
60 plus	65	53	81.5	46	34	73.9
Totals....	2,019	512	25.4	2,371	596	25.1

Tuberculin at Hagerstown, Maryland (4). Old Tuberculin gave definitely higher rates among school children, but among the more sensitive adult population the differences were small. There is apparently no significant difference in sensitivity between males and females.

The incidence of definite calcification regarded as healed primary tuberculosis is shown by age and sex in chart 2. Most of the calcification develops at an early age; the incidence in our 5–9 year age group was 27 per cent and 31 per cent for boys and girls, respectively. The youngest child in whom we found definite calcification was two years of age. The fact that the incidence is somewhat less rather than more in the

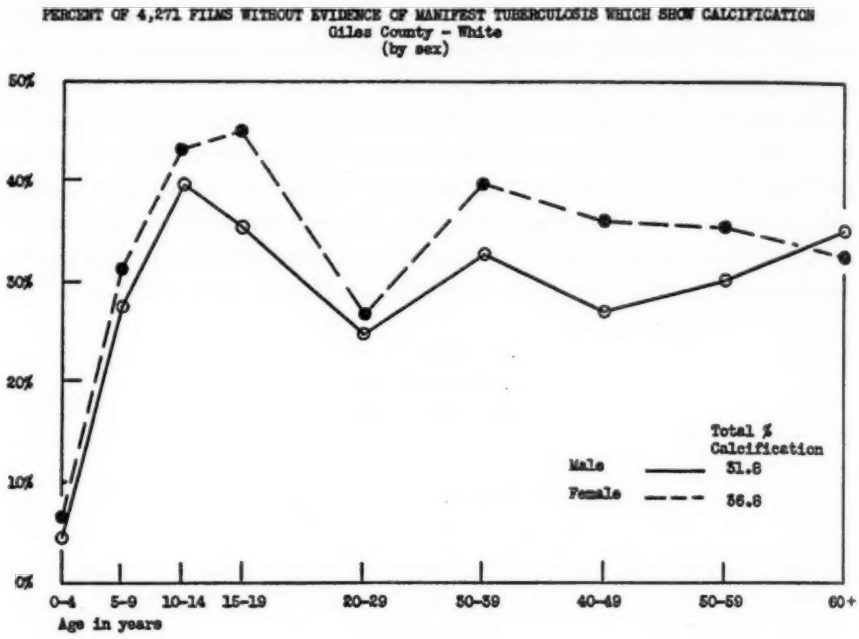

CHART 2

TABLE 2

Per cent of 4,271 films without evidence of manifest tuberculosis which show calcification

Giles County—White

(By sex)

AGE	MALE			FEMALE		
	Total	Calcification		Total	Calcification	
		Number	Per cent		Number	Per cent
years						
0–4	73	3	4.1	65	4	6.2
5–9	460	126	27.4	467	144	30.8
10–14	559	222	39.7	678	290	42.8
15–19	330	117	35.5	408	183	44.9
20–29	185	45	24.3	259	68	26.3
30–39	144	47	32.6	178	71	39.9
40–49	93	25	26.9	136	49	36.0
50–59	70	21	30.0	73	26	35.6
60 plus	56	20	35.7	37	12	32.4
Totals....	1,970	626	31.8	2,301	847	36.8

adult age groups suggests that it is not a cumulative phenomenon that continues to develop throughout life, but a response to some experience, such as first infection with tuberculosis, which occurs in most of the population at an early age and is not repeated. The decrease in incidence with age suggests that some of the lesions may be resorbed. Females show consistently higher rates than males except in the oldest age group, whose rates are based on only 93 examinations. Total incidence was 31.8 per cent and 36.8 per cent for males and females, respectively, as compared with Gass's finding of 50 per cent in Williamson County.

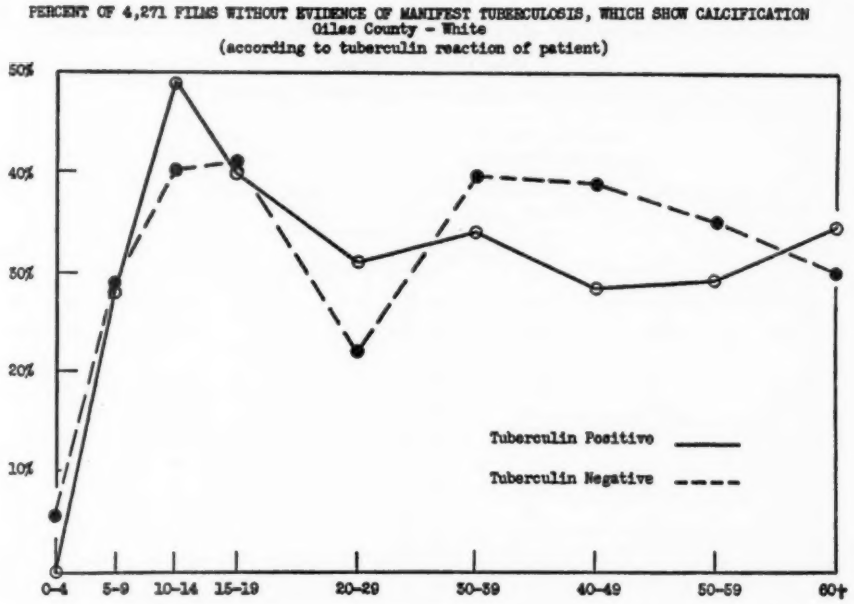

CHART 3

Gass, however, re-X-rayed in oblique positions all lesions that were doubtful on the flat plate and confirmed many that would have been excluded from our series.

Chart 3 shows the incidence of calcification according to the tuberculin reaction. The total incidence was 35.4 per cent among tuberculin-positives and 34.2 per cent among tuberculin-negatives. This slight difference corresponds with Gass's finding of 51.1 per cent and 48.1 per cent in positive and negative reactors, respectively. The curves indicate furthermore that this lack of specificity of tuberculin for calcification occurs at all ages.

Chart 4 shows the number and distribution of lesions in the two lungs. Remembering that no attempt was made to describe every shadow that might indicate a lesion, it is still possible to obtain a good indication of the distribution and a fair indication of the number from an analysis of our definitely described calcifications. Films showing a single focus in the peripheral lung field and calcified lymph nodes in the corresponding hilum were counted as single lesions or complexes. All films showing lesions of any sort on both sides, or more than one lesion

TABLE 3

Per cent of 4,271 films without evidence of manifest tuberculosis which show calcification

Giles County—White

(According to tuberculin reaction of patient)

AGE	TUBERCULIN NEGATIVE			TUBERCULIN POSITIVE		
	Total	Calcification		Total	Calcification	
		Number	Per cent		Number	Per cent
years						
0–4	128	7	5.5	10	—	—
5–9	871	254	29.2	56	16	28.6
10–14	1,071	430	40.1	166	82	49.4
15–19	598	244	40.8	140	56	40.0
20–29	278	61	21.9	166	52	31.3
30–39	138	55	39.9	184	63	34.2
40–49	84	33	39.3	145	41	28.3
50–59	45	16	35.6	98	31	31.6
60 plus	20	6	30.0	73	26	35.6
Totals....	3,233	1,106	34.2	1,038	367	35.4

in the peripheral lung field, were counted as multiple. There were 22.7 per cent of such films. Twelve cases showed so many small, round lesions of uniform size scattered evenly throughout both lungs that they were classified as diffuse or healed miliary. The 86.8 per cent unilateral lesions were distributed with 51.9 per cent on the right and 34.9 per cent on the left side. The proportion of multiple lesions was about the same on the right and left.

Chart 5 shows the distribution of the single lesions in the various lung fields. The majority on each side were in the lower lung field. The

obscuring of part of the left lung field by the cardiac shadow artificially decreases the number of lesions recognized on this side.

In view of the suggestion that the high incidence of calcification among tuberculin-negative individuals in our study area may bespeak some local cause other than tuberculosis, it is of interest to compare the clinical characteristics of our cases with those found elsewhere.

German workers have devoted considerable study to this subject following Gohn's classical observations. Beutel (5) in 1930 reviewed the

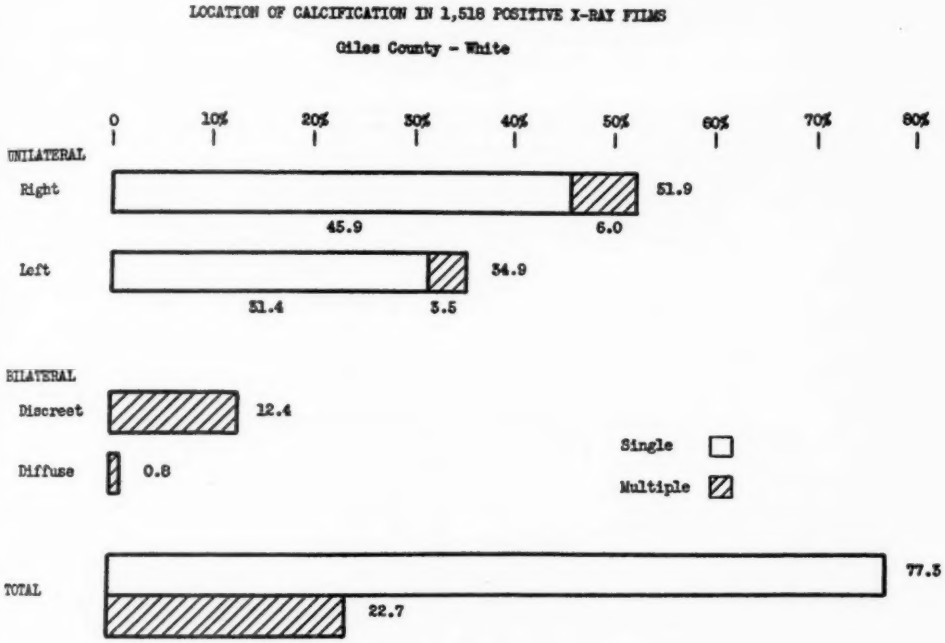

CHART 4

literature, and found a rather remarkable consistency of clinical findings. Six different observers reported from 60 to 67 per cent of roentgenologically demonstrable calcifications on the right side as compared with our 59.8 per cent. Gohn, by autopsy, found 55.5 per cent of primary foci on the right. Four different observers reported from 22 to 28 per cent of their positive films with multiple calcifications, as compared with our 22.7 per cent. Lüders (6) reported 94.7 per cent of her positive films to show multiple lesions, but these were routine hospital films, over

20 per cent with reinfection type tuberculosis, calcification of which she did not classify separately. Three observers found a higher incidence in females than males, and two found lower, as compared with our incidence of 31.8 per cent in males and 36.8 in females.

With regard to the distribution of lesions in the various lung fields, Beutel classifies 61 lesions which he considers on the basis of X-ray to be calcified primary foci. Lüders, on the other hand, reports the distribu-

TABLE 4

Location of calcification of 1,518 positive X-ray films

Giles County—White

	SINGLE		MULTIPLE		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Unilateral						
Right lung	697	45.9	91	6.0	788	51.9
Left lung	477	31.4	53	3.5	530	34.9
Bilateral						
Discreet	—	—	188	12.4	188	12.4
Diffuse	—	—	12	0.8	12	0.8
Total	1,174	77.3	344	22.7	1,518	100.0

Location in lung fields of 1,174 single lesions

	RIGHT		LEFT	
	Number	Per cent	Number	Per cent
Upper lung field	134	19.2	106	22.2
Middle lung field	164	23.5	103	21.6
Lower lung field	276	39.6	197	41.3
Hilum	123	17.7	71	14.9
Total	697	100.0	477	100.0
Total single 1,174	697	59.4	477	40.6

tion of all calcified lesions, including reinfection type, in her series of 1,190 positive films—all on hospital patients.

	BEUTEL	LÜDERS	LUMSDEN, *et al.*
	per cent	*per cent*	*per cent*
Upper lung field	44	45.5	24.6
Middle lung field	23	27.6	27.2
Lower lung field	33	26.9	48.2

Comparison of results shows Beutel and Lüders to have 44 and 46 per cent respectively in the upper lung fields as compared with our 25 per cent, and 33 and 27 per cent respectively in the lower lung fields as compared with our 48 per cent. These percentages suggest on their face a larger proportion of basal lesions in our series, but the smallness of Beutel's series, the inclusion by Lüders of reinfection type lesions, the lack of definite boundaries between the various lung fields and the im-

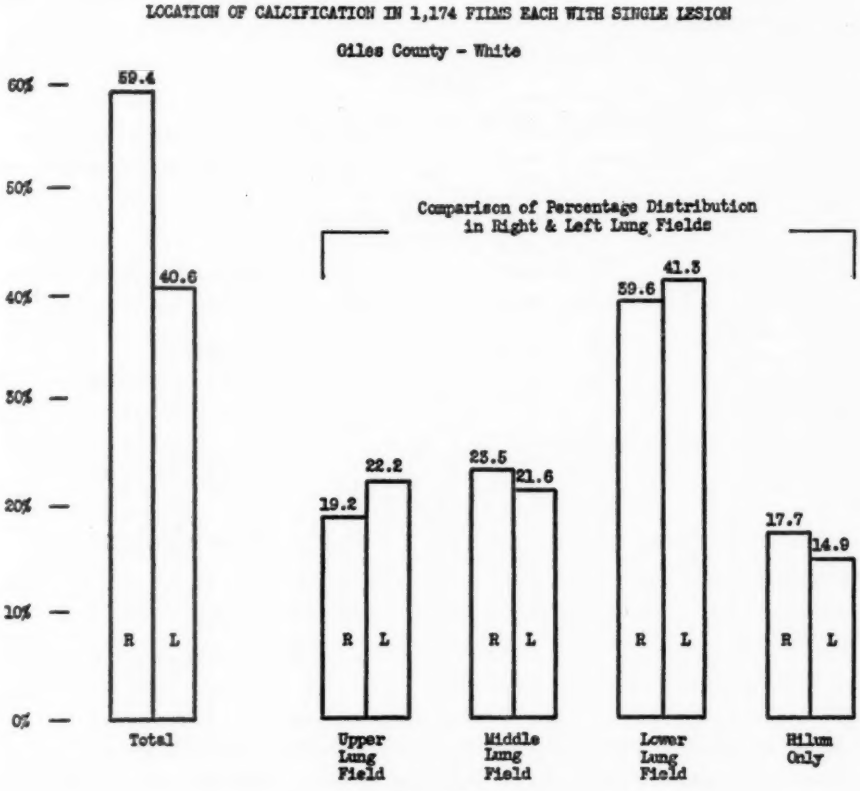

CHART 5

possibility of always distinguishing between hilum and parenchymal calcification in the lower zones make the differences appear of less significance. The incidence of tuberculin reactors, moreover, is about the same in our series among individuals with variously located calcified lesions; single lesions in the upper, middle and lower lung fields gave 24 per cent, 25 per cent and 24 per cent reactors, respectively, and multiple lesions supposedly less typical of primary tuberculosis gave 28 per cent.

There is, then, no indication from a clinical analysis of the 1,500 calcified lesions from Giles County that aetiologies other than tuberculosis are importantly operative. The lesions have the same clinical characteristics as to number and distribution in the lungs as have been repeatedly found in series where the accepted aetiology was tuberculous. The implication is, rather, that the tuberculin test is not specific for these lesions. Detailed pathological, bacteriological and clinical studies, now in progress, are necessary, however, before their significance can be finally determined.

TABLE 5

Distribution of calcified foci found by various workers

AUTHOR	NUMBER OF CASES	RIGHT LUNG	LEFT LUNG	MULTIPLE LESIONS	METHOD OF EXAMINATION
		per cent	*per cent*	*per cent*	
Beutel (5)	70	64.6	35.4	—	X-ray
Beutel (5)	96	64.9	35.1	—	Postmortem X-ray
Lüders (6)	1,190	60.4	39.7	94.7	X-ray
Gohn*	511	55.5	44.22	—	Autopsy
Nüssel	300	64.3	35.7	—	X-ray and fluoroscopy
Baer	75	65.3	34.7	—	?
Knusli	521	63.3	36.7	25	?
Wiese	185	66.5	33.5	—	Fluoroscopy and X-ray
Ballin	140	—	—	22	X-ray
Müller	144	—	—	22	?
Ickert	779	—	—	28.2	X-ray and fluoroscopy
Lumsden, Dearing, Brown	1,518	59.8	40.2	22.7	X-ray

* Remaining authors quoted by Beutel (5).

Our tuberculin findings with regard to X-ray shadows of potential clinical significance were of a different order. Among 4,377 subjects tuberculin tested, were 57, or 1.3 per cent, with shadows regarded as characteristic of reinfection type tuberculosis. Of these, 10, or 0.3 per cent, were among the 3,270 nonreactors, whereas 47, or 4.2 per cent, were among the 1,107 reactors to 0.000,5 mg. of PPD.[3] Of the 10 nonreactors,

[3] The different age distributions of reactors and nonreactors, however, magnify this apparent selectivity of the tuberculin test; less than one-fourth of the positive reactors were under fifteen, whereas nearly half of the nonreactors were in this age group, where reinfection tuberculosis is rare.

8 were re-X-rayed and examined clinically from two to ten months later by the Tennessee Diagnostic Clinic, and two (both under twenty years of age) were reclassified—one as nontuberculous, probably fungus infection, and the other as epituberculosis, since her lesion, originally characteristic of a primary infiltration, had disappeared without any trace. Of the remaining 6 reëxamined nonreactors, one was far advanced and died six months later, whereas the other 5 continued to manifest positive X-ray findings and 3 had râles over the site of the lesion. One of the 2 who were not reëxamined had been diagnosed tuberculosis clinically thirty years ago; the other had a typical, old, infraclavicular lesion with some calcium deposition. All 7 were considered as of doubtful activity; one was aged twenty-nine and the other 4 ranged from forty to seventy-five.

Of the 47 tuberculin-positive cases, 25 had reëxaminations, which, in every case, confirmed our findings and diagnosis. Furthermore, two high school girls, both with four-plus tuberculin reactions but negative X-ray films at our examination, were reëxamined and had developed minimal and moderately advanced lesions, five and ten months later, respectively.

Questionable reinfection type tuberculosis was our finding on 4 cases which were later reëxamined. One was tuberculin-negative and was finally classified as bronchitis; of the 3 who were positive, 2 were classified as tuberculous and one as probably lung abscess.

Of 5 classified as childhood type tuberculosis, one was tuberculin-negative, but was not reëxamined. Another tuberculin-negative child, whose film showed a questionable childhood type lesion, had developed tracheobronchial calcification with clearing of her infiltration, three months later.

To summarize: Among the tuberculin-negative individuals, 8 cases of presumable reinfection type tuberculosis were found, one of whom has since died and 6 of whom have had a diagnosis of chronic fibroid tuberculosis confirmed on independent examination. Among the tuberculin-positives, 47 cases of reinfection type tuberculosis were found, 25 of which were confirmed by reëxamination. Two of 3 questionable cases were confirmed on reëxamination, and 2 new cases developed. This totals 51 reinfection type cases to date among 1,107 tuberculin reactors, or 4.6 per cent, as compared with 8 among 3,270 nonreactors, or 0.2 per cent.

The clinical classification of these 59 cases was as follows:

	TOTAL	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED	
		Number	Per cent	Number	Per cent	Nu ber	Per cent
Tuberculin negative.....	8	6	75	1	12	1	12 (Fatal)
Tuberculin positive.....	51	29	57	18	35	4	8

Apical salients or irregular pleural caps were found on 20 films—9 in tuberculin-negative reactors and 11 in tuberculin-positive reactors, an incidence of 0.3 and 1.0 per cent, respectively, among nonreactors and reactors. Twelve of the 20 were over forty years of age. This fact plus the tuberculin findings raises a question as to the specific tuberculous aetiology of these lesions, especially in view of the finding of Davson and Susman (7) that many apical scars in old persons have nodules characteristic of silicosis rather than tuberculosis.

The finding of more than twenty times the incidence of reinfection type lesions among reactors to a single dose of 0.000,5 mg. of PPD indicates this method to be an efficient screen in practical case-finding. It raises a serious question, moreover, whether the extra expense of two-dose testing is justifiable in mass screening.

Finally, it remains to be pointed out that any program which depends on the tuberculin test to select individuals for further examination thereby eliminates a definite, often large, proportion who refuse the needle. McKneely (8) at Hagerstown, Maryland, obtained consent for only about 60 per cent of school children. The administrative problem then confronts us whether to eliminate the untested group from further study, or to put a premium on refusal of the test by X-raying all who decline to be tested.

CONCLUSIONS

1. A single-dose Mantoux test with 0.000,5 mg. of PPD in Giles County, Tennessee, selected 25 per cent of 4,400 individuals among whom were 86 per cent of those who had or developed within a year apparent reinfection type tuberculosis demonstrable on X-ray examination.

2. Single-dose Mantoux testing is a reasonably efficient screen for case-finding where the cost limits the number of X-ray examinations, but the X-ray is still the basic tool in case-finding.

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MASS TUBERCULIN TESTING AND X-RAYING[1]

CHARLES L. IANNE[2]

Doctor Long has quite thoroughly covered the field as to the value of tuberculin from both a clinical and epidemiological view. To a clinician the practical implications are most important. So, for purposes of follow-up, I take it for granted that once a reactor, always a reactor. Here I would like to interject the record of two bizarre reactions to the tuberculin test that have come to my attention, and were discussed with Doctor Long and most of the pathologists present, without securing an answer. The last word on the tuberculin reaction has not been said.

Case 1: A teacher in our sanatorium, although a negative reactor, had a large calcification in the left hilum. Despite ten years of sanatorium work she remained a negative reactor to all dilutions of OT and PPD, annually.

Case 2: A student nurse had no reaction to three dilutions of OT until six weeks after tests were done, when definite one- and two-plus reactions showed at sites of injection. Evidently infection had occurred in the meantime and caused a reaction to unabsorbed tuberculin. A subsequent tuberculin test substantiated the fact that infection had occurred.

Doctor Doull demonstrated by algebraic figures that case-finding by tuberculin testing school children is very expensive. The Santa Clara County Tuberculosis Association, in coöperation with the Health Departments, has been tuberculin testing high school children since 1934. The Association has an automobile trailer which it lends to the Health Departments for X-raying reactors. To date 13,468 have been tested and 54 cases of reinfection type have been found by this method.

In 1938 the Tuberculosis Association added a public health nurse, trained in tuberculosis field work, to assist in the follow-up of families in whom tuberculin reactors were found. Out of 560 families contacted, 7 cases were found by this worker at a cost of $1,479.94 or $211.42 per

[1] *Discussion* of papers presented at a Symposium on *Mass Tuberculin Testing and X-raying* at the 35th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, June 29, 1939.

[2] Santa Clara County Sanatorium, San Jose, California.

case. This investment is definitely worth while as compared to the cost of hospitalization of even one of these cases if not found until after symptoms occur—not taking into consideration the fact that we are preventing further infection of the household and community.

Doctor Douglas has explained and demonstrated the photographing of the fluoroscopic image. This should reduce the cost of X-raying and give permanent record of the fluoroscopic picture to compare with future X-ray films, whereas the fluoroscope alone gives no permanent record for comparative study.

As Doctor Douglas mentioned, the fluoroscope and X-ray film tell either too much or too little. The latter is the point I wish to stress. The fluoroscope and X-ray film do not reveal infection until after it has caused a shadow in the lung. Therefore the fluoroscope and X-ray film without tuberculin test leave the majority of infected families without follow-up and prevention of disease. To illustrate: A prenatal case had positive tuberculin test but a negative X-ray film. Because of the tuberculin reaction the other members of her family were carefully checked. The husband was found to have an occult minimal tuberculosis with positive sputum. Had we used only the fluoroscope or X-ray film as a basis for our examination of the prospective mother, the infant would have gone into the home of a tuberculous father and the far-reaching results can be imagined.

Instead of trying to discover the case we have allowed through ignorance or negligence to become infected, we are now placing the emphasis on the prevention of infection, which is the basis from which to work in order to reduce tuberculosis to nil as a cause of death.

It seems logical to begin this campaign with the prospective mother. By tuberculin testing all prenatals and X-raying those who react and carefully checking these families, we may prevent infection of the new generation. In June, 1936, we began tuberculin testing prenatals entering the Santa Clara County Hospital. This was prompted by the seemingly unnecessary death of two young mothers (after costing the county $5,000 for hospitalization), who left behind small families of infected children.

We have found the cost of $176.71 for each case to be relatively very low, in view of the fact that whole families are protected from infection by the mother through this simple procedure. The above figure is not much above the average as shown by Plunkett[3] in his selected group.

[3] Case-Finding, American Review of Tuberculosis, 1939, *39*, 256.

Between June 1, 1936 and June 1, 1938, 805 women in the so-called "dangerous" age were tested; 691 tests were read; 284, or 41 per cent, reacted to Old Tuberculin 1:1000. Of the reactors, 252 were X-rayed; 32 failed to return. The X-rays revealed 10 cases of minimal tuberculosis, one moderately advanced and one far advanced. Nine were admitted to the sanatorium before or immediately after delivery, and pneumothorax was established in seven. Two had phrenic paralysis when a free pleural space was not found. Three with inactive lesions were treated at home.

None of the reactors, including those with lesions, have had extension or clinical manifestation of disease. Most of the mothers with satisfactorily established pneumothoraces are home caring for their families. Only one of the children has been infected to date. It is gratifying to note that there have been only two deaths in the first year of life since 1934 in Santa Clara County, a mixed urban and rural population of 160,000. These occurred in 1935. In 1937 there was only one death in the age group from one to ten years.

CONCLUSIONS

1. The routine use of the tuberculin test in prenatal care is a method that can be easily used in clinics and private practice for discovery of active tuberculosis.

2. Forty-one per cent of patients who returned for reading had positive tuberculin tests.

3. Unsuspected, active tuberculosis occurred in 1.7 per cent of those read. These were isolated to protect the patient and hospital personnel.

4. The cost of fluoroscoping or X-raying the tuberculin reactors would be very little more than the cost of routine Wassermann.

5. Early diagnosis permits early institution of collapse therapy, thus permitting pregnancy to continue without extension of pulmonary disease.

6. Although this is a small group and the time elapsed is short, the findings are of sufficient public health value to recommend it as a routine preventive measure. *Prevention of tuberculosis should begin before birth.*

FLUOROSCOPY IN CASE-FINDING[1]

J. RODRÍGUEZ PASTOR[2]

In Puerto Rico we do not usually apply the tuberculin test to persons above twelve years of age, because extensive tuberculin surveys in our island have shown that at the age of twelve more than eighty per cent of children react to the tuberculin test, while beyond the age of fourteen over 90 per cent react and by the age of twenty practically every one is a reactor.

Our procedure for case-finding consists in fluoroscopic examinations complemented by X-ray plates of suspicious or positive cases.

I fully agree with Doctor Long that the tuberculin test has been proved beyond any reasonable doubt to be a reliable index of tuberculous infection. I can easily understand its great value as a diagnostic agent in communities with a low incidence of tuberculous infection. However, in a community like ours, where tuberculin allergy is almost universal in adolescents and adults, the tuberculin test has very little value as a diagnostic procedure beyond the age of ten. Fluroscopic examinations are a very satisfactory and quite inexpensive substitute. The importance of fluoroscopic examinations as a diagnostic procedure can hardly be overestimated. I do not believe this procedure has yet been given its proper place in case-finding campaigns in this country. In Puerto Rico the Health Department is making fluoroscopic examinations available in every corner of the island. We are installing fluoroscopes in every Public Health Unit. Lately, we have been using our fluoroscopes for the taking of X-ray plates, and we are getting very satisfactory results. A timer and a cassette stand are about the only extra equipment needed to convert a 30-milliampere fluoroscope into a radiographic machine for case-finding purposes. We make our own casette stand and a timer can also be improvised. A fluoroscope is probably the best investment that any community of limited resources can make to help

[1] *Discussion* of papers presented at a Symposium on *Mass Tuberculin Testing and X-raying* at the 35th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, June 29, 1939.

[2] Department of Health, San Juan, Puerto Rico.

combat tuberculosis. As an aid in case-finding, there is no other single piece of equipment that can compare with it.

Doctors Ordway and Fellows state that among 25,000 subjects fluoroscoped at the medical offices of the Metropolitan Life Insurance Company the average cost of a fluoroscopic examination was fifteen cents. They also found that an accurate diagnosis as to the presence or absence of pulmonary tuberculosis could be made with the fluoroscope alone in 87 per cent of 2,603 persons examined. I do not know of any other diagnostic apparatus available that could give us such a high percentage of accurate diagnoses at so low a cost.

There is fear of the fluoroscope among general practitioners because of an exaggerated notion of the harm that may come from its frequent use. The modern fluoroscopic apparatus is so well protected that the danger from an overdose of X-ray through its use is practically negligible. There is need of an educational campaign among physicians in this respect. In Puerto Rico we are beginning to train every medical health officer in the use of the fluoroscope. No medical office should be without this indispensable diagnostic equipment. A more extensive use of the fluoroscope by the general practitioner could be an immense help in the fight against tuberculosis.

This, I believe, should become a slogan among tuberculosis workers: *Use the fluoroscope more!*

FATEFUL PERIODS IN THE LIFE OF THE TUBERCULOSIS-INFECTED INDIVIDUAL

JULIUS HOLLÓ

Under the civilized conditions of our time the fate of the tuberculous individual depends largely on his behavior during certain, mostly short, periods of life. I should like to present evidence for this statement, together with some practical corollaries.

The yearly death rate from tuberculosis has for the last fifty years shown a rapid and progressive decrease. This decrease, especially in the wealthier and more civilized countries, and even more so in their big cities, brought the mortality rate of tuberculosis down to a level that surpassed the expectations of the greatest optimists. Between 1880 and 1890, when the statistical study of mortality from tuberculosis had gradually become an international scheme, the gross average of mortality from tuberculosis in large civilized cities was about 40 to 50 deaths yearly for every 10,000 of the population. From then until 1914 this number went down about 50 per cent. During the Great War there was a definite set-back all over the world and some cities, for example Berlin and Budapest, were thrown back to the level of the eighties of the last century. Fortunately, this relapse was short and since that time the rate has decreased more rapidly than at any other time before. At present the mortality rate for tuberculosis in large cities ranges from 5 to 10 per 10,000 and there is a definite trend toward further reduction.

Now what may be the cause of this world-wide decrease of mortality from tuberculosis? The development of therapy is by no means responsible. It is true that with an optimal and thorough combination of sanatorium and really up-to-date collapse treatment the percentage of cures in open phthisis could be raised to about 40 to 50 per cent, as compared to an average of 15 to 20 per cent obtained under sanatorium treatment only. These extraordinary results, however, were obtained only recently and in a few exemplary sanatoria of the United States. It is obvious that the former less effective hospital and pneumothorax treatment could not noticeably affect mass statistics, since even to-day

they are available only to a small part of the population, and the situation was far worse twenty and thirty years ago.

Nor is the decrease in number of tuberculous individuals of great importance. Of course, it is a fact that nowadays fewer people suffering from consumption are seen in hospitals and clinics. It should be borne in mind, however, that "tuberculosis" does not necessarily mean a gross anatomical lesion, but a tuberculous infection contracted at any time in the past. With very few exceptions, those once infected remain infected all their lives. Their calcified primary complexes harbor virulent bacilli, and from their seemingly encapsulated foci microscopical channels lead to the organism. The number of accidental postprimary tuberculous findings increases considerably with the length of time elapsed since the occurrence of the infection and in autopsies of aged individuals old foci showing signs of recent activation are remarkably common incidental findings. Therefore in most cases it is more correct to speak of a slowly progressing, chronic tuberculosis than of an inactive tuberculosis, even though our present diagnostic methods may show no anatomical lesions or indications of activity during the short time of observation generally available.

Of course, if tuberculosis is defined as above, its frequency can be measured not by the number of hospital patients nor by gross lesions, but only by the frequency of positive tuberculin reactions. Recent investigations have shown that nowadays in civilized countries the proportion of adolescents reacting to tuberculin is much lower than it was in the years before and immediately after the War. In the United States for example, a significant part, probably even the majority of the population, passes puberty without having been infected with tuberculosis, and conditions are still improving. This fact may prove of decisive importance within the coming decades. It is however by no means marked enough and mainly too recent to account for the great decrease in mortality.

The rapid fall in mortality can be explained neither by the remarkable results of modern therapy nor by the obvious decrease in the number of the infected, but above all by the simple fact that the course of tuberculosis, in the meaning of a chronic infection, not of a clinical disease, has become successively milder, more delayed than it was before. Its progress is slower now, its moves are scarcer and less apt to attain the intensity of a clinical disease.

This mitigation of the course of the infection cannot be explained by

an alleged dying out of the more sensitive part of the population, nor by a never-proved inheritance of immunity, nor by a decrease in virulence of the pathogenic microörganism. Detailed statistics definitely refute these alluring theories. The changes are far too sudden and incongruous in different nations or in different social classes and age groups of the same population and are far more reversible, as evidenced during and after the Great War, to be accounted for by the theories mentioned. The causes must be entirely different.

An analogy may shed some light on the situation. It has been observed many times that rats—in contrast to other animal species—do not tolerate splenectomy well. A few days after the operation they will become sick, lose weight, and most of them will die quite soon, showing symptoms of profound anaemia. Surprisingly, their anaemia exhibits all the typical features of the infectious anaemias. The solution of this puzzling observation is simple. It happens that most rats are infected by a microörganism belonging to the group Bartonella. The infection, however, remains latent and the presence of the microörganism is harmless until splenectomy radically changes the situation. The Bartonellas leave their hiding places, invade the blood, destroy the red cells and make the animal, seemingly healthy before, seriously ill. Arsphenamine will kill the Bartonella and rats pretreated with arsphenamine will not become ill after splenectomy. With this fact known the rôle of the Bartonella in the postsplenectomy anaemia of rats has been definitely established.

In human tuberculosis, conditions are similar. Under physiological, that is, favorable, conditions, infection with tuberculosis, as a rule, does not involve serious danger. If, however, resistance is broken by some additional factor (like splenectomy in rats), infection will progress and finally defeat the organism. In most cases the tuberculous disease is the effect of certain factors besides infection.

At present many of these harmful influences are known. The material of recent statistical compilations gives ample opportunity to compare mortality rates of human groups living under the most diversified conditions. Careful study shows that malnutrition, overexertion and lack of pure air are the chief catalysts of tuberculosis, to which one may add the lack of hygienic culture, especially in groups living in infected environment.

In the middle of the last century the overwhelming majority of the city population had an insufficient and ill-balanced diet, they were overburdened by work, lived in crowded, filthy, poorly ventilated rooms and

had almost no access to fresh air, water or sunshine. This explains the rich harvest of tuberculosis at that time. The situation has considerably changed since, and this change accounts for the great improvement in the mortality rate. In our days large masses of the population live under wholesome conditions, their working time does not exceed forty to fifty hours per week, their food is plentiful and of good quality, their rooms are spacious, well aired, they have a feeling for cleanliness, they know the elementary facts about hygiene and they spend their spare time in healthier ways.

If the comparatively few, who, on account of their special disposition, their infected environment and poverty, form a separate group, are disregarded, the rest of the population in the normal periods of their lives are not as a rule exposed to privation that could be dangerous in regard to their latent tuberculosis. It would be, however, a delusion to believe that these privations and dangers have completely disappeared from the lives of the masses. They are still present, but with a very essential difference. Formerly they existed continuously all through the course of life, like milestones along a highroad, whereas now they are present, like a few warning signs, only at particularly dangerous curves on the path of life. It is at these points where it will be decided whether a chronic tuberculosis will keep within its previous benign course or whether it will dash on and precipitate its victim into an abyss. These are the fateful periods under discussion.

In the years around the Great War the start of a tuberculous disease could but occasionally be traced back to some well defined indiscretion in life habits. Frequently, the patient sought medical attention after the lapse of a long period of time following exacerbation of the disease; diagnosis was rather uncertain; and privation was so organic a part of life that it was difficult to find any specific eliciting cause. Now, however, the connection between some harmful influence and the apparent start of the disease is quite obvious in most cases. Among the events which in my experience have given rise to manifest disease or to flare-up of a quiescent condition, the following ones may be listed:

College and university examinations
Military service
Training for athletic competition
Excursion connected with mountain climbing
Camping

Excessive sun-baths
Opening of a shop
Failure in business
Seasonal overwork (tailor, furrier, farmer)
Preparation for a new rôle on the stage
Exhaustive work of a physician during an epidemic
Acceptance of an additional job
Nursing of the gravely ill mother
Love affairs
Honeymoon
Abortion
Childbirths in quick succession
Divorce proceedings
Death in the family
Weight reducing cure
Tonsillectomy
Drastic antisyphilitic treatment
Intercurrent diseases (measles, whooping cough, diabetes, coronary thrombosis, and especially suppurations of the lungs)

Another group of fateful periods in the life of the tuberculous patient is characterized by oversensitiveness to harm, which may be a feature of certain age periods or may be linked with certain phases of the infection.

It appears that the periods of infancy and senility rather than puberty represent the most susceptible periods for tuberculosis (1). It is true that at puberty a relatively large number of cases of phthisis show an acute course, but this is due to reasons other than increased susceptibility. Many adolescents are under great physical or mental strain aggravating the known emotional difficulties of this age period. They miss the parental supervision they had enjoyed in childhood while they are yet unable properly to take care of themselves. Often they exchange their home with an unfavorable, and possibly infected, environment. Furthermore, the number of mild, chronic cases of phthisis is relatively small at puberty; such forms are not likely to manifest themselves before the patient reaches a higher age.

In senility the reverse is true. The frequency of acute or reactivated forms in this age period is obscured by the great number of chronic cases that are carried over from earlier periods of life. At the same time, the rapid increase of other causes of death in old age brings about a proportional decrease of the mortality rate from tuberculosis. These facts

account for the erroneous belief in the relative immunity of old people against tuberculosis. As a matter of fact, old age is remarkably defenseless against tuberculosis as well as against most diseases. Mortality statistics, autopsies and clinical observations equally prove a rich harvest of tuberculosis in old age. Some of the factors that may play a rôle are defective nutrition, indoor life, psychic depression, relative strain and the weakening diseases that often accompany old age. The main cause, however, is the decreased resistance of the old organism.

The plight of infancy is even worse. The yearly fatality rate from tuberculosis, that is, the percentage of deaths among the infected for every year, is about fifty times higher in the first year of life, than the average yearly fatality of the same population; and in the first half year of life the data are even more appalling (1). Contributing factors are the higher and often unsatisfied need of the infant for nutrition, cleanliness and nursing care. Furthermore, a relatively large percentage of the infections in infancy are intradomicilary, that is, mostly massive infections. The special constitution of the infant, the undeveloped condition of its defense mechanisms is probably a decisive factor. Moreover, infection in the infant is invariably a fresh one, whereas in later periods of life the number of old infections steadily increases. With this statement we are turning to the the third group of fateful periods.

The fatality of tuberculosis in the first year following the infection, at any age, greatly exceeds that of all the later years, following the infection (1). The course taken by the disease in its first year seems to be of decisive importance to the life of the infected individual. The first stage of the infection, the so-called stage of generalization, is dominated by the primary complex and its lymph node component. The latter are centres for further attacks. In severe cases the contents of the caseous lymph nodes may break into the neighboring blood vessels and lymphatics and in this way give rise to generalized tuberculosis. It is known that 60 to 70 per cent of all cases of acute miliary tuberculosis and tuberculous meningitis occur in the first year following infection. The course of disease is much less dramatic if the infection reaches the blood-stream after a slow spread from one lymph node to the other, only a small number of bacilli getting into the circulation at one time and setting up small, usually microscopical lesions in distant organs, particularly in the lungs. These secondary lesions may later form the starting point of a new spread. In favorable cases—probably the majority—the infection does not pass beyond the lymph nodes, this fact greatly improving the

prognosis of the disease. Too the danger of a further spread or flare-up of the process becomes minimal after macroscopical healing of the primary complex, if no distant lesions have formed in the meantime. However, the healing of the primary complex usually requires about one to two years. During this time, especially during the first months, the infected individual needs exceptional care, not only because this is the time that the first seeds are sown, but also because a fresh caseous inflammation is highly sensitive to the slightest disturbance and its reaction may prove disastrous.

The majority of the later consumptives emerge from the first phase of infection with certain defects. In these individuals the X-ray picture shows, beside the primary complex, perihilar scars, calcified lymp nodes, pleural bands and adhesions or small foci scattered throughout the lungs, often in the apices. Group examination of young adults is likely to show such lesions in about 5 to 10 per cent. The subjects are not ill but obviously belong in the group of the threatened, of the hypersensitive. They need special protection against harmful influences. This protection may be of vital importance in those, unfortunately not too rare, periods when one or the other of the foci shows signs of activation or when fresh dissemination takes place. In these periods the start of an open consumption may hang by a hair.

I have finished the enumeration of the fateful periods. As to the proper plan for dealing with them, it should be mentioned, first of all, that some of them can be avoided (foolish reducing cures, excessive physical exercise, heedless sun-bathing). In other cases at least superimposition of harmful influences can be prevented. Thus, when nursing a patient or preparing for a school examination one should observe the rules of proper nutrition, take short daily walks, etc. Parents, husbands, wives, teachers, employers should be taught the possible disastrous consequences of overexertion.

Attention should be paid to the nutrition of old people; hard work, especially hard physical work, is to be avoided in this age. Infants have to be protected against infection at any price. This is possible in most cases, even if the parents are infected. Needless to say, infants require good nursing including a liberal air supply.

No individual who is uninfected should accept any job which entails the danger of a massive infection. Doctors and nurses, before they go to serve in a tuberculosis department, should be tested with tuberculin. Systematic tuberculin tests are a part of the conscientious care of children.

With the aid of the tuberculin test it is possible not only to discover the fact of infection but quite often also to determine the time when it occurred. In this way fresh infections can be recognized and treated at once. The nucleus of the treatment should be strict bed-rest ranging, depending on the severity of the case, from a few weeks to several months. The patient should be declared cured only on the basis of serial X-ray pictures. The treatment of the primary infection is the only early treatment of tuberculosis and the most effective one.

In the same way every patient with any possible activation of a tuberculous process should be put to bed at once. Patients with quiescent, slight changes that can be shown roentgenologically to be beyond the primary complex should lead a life free from stress and privation; before engaging in any kind of obligation involving stress, such as school examinations, military service, strenuous sport and so on, an X-ray examination is highly advisable. Fortunately, the public is increasingly becoming conscious of this. Of course, the ideal procedure would be to keep every individual from childhood throughout life under constant X-ray and tuberculin control. This is the only way to obtain a complete and dependable picture of the events that occur in the organism. On the basis of these findings the burden-bearing capacity of the infected individual can be assessed with fair accuracy. I think nowadays most parents can easily be convinced of the importance of this control.

SUMMARY

The gravity of a tuberculous infection has greatly decreased in the course of the last decades. The normal periods of our present civilized lives do not involve any material danger of activating a quiescent tuberculous focus. The dangers and harms are confined to comparatively short periods of life and can thus frequently be avoided by caution and care.

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HAEMATOGENOUS TUBERCULOSIS IN THE ADULT[1, 2]

II. Haematogenous Pulmonary Tuberculosis

ELI H. RUBIN

When one analyzes a large number of cases of haematogenous tuberculosis in the adult, one finds that the lungs are almost invariably involved to a greater or lesser extent but that in many instances other organs escape significant infection. This is true at necropsy as well as clinically and applies to some degree to all forms of the disease excepting a small percentage of so-called "surgical" forms of tuberculosis. For some reason or other, when tuberculosis involves extensively an extrapulmonary organ or a group of organs, such as the urogenital system, the osseous system, serous membranes, etc., the lungs are apt to escape with a minimum of destructive changes (15). In considering, therefore, the development of haematogenous tuberculosis in the lungs, two problems arise which are of particular interest from a clinical standpoint: (*1*) Under what conditions does haematogenous tuberculosis affect mainly the lungs? (*2*) Are there any means of differentiating haematogenous pulmonary tuberculosis with the lungs the dominant seat of localization, from that in which the lungs are involved as part of a systemic tuberculosis? Since, on the one hand, one is dealing with a blood-borne infection and, on the other, an organ with a dual circulation, an answer to these problems might profitably be sought first in the anatomical distribution of the blood vessels of the lungs. Obviously, distinguishing characteristics, if any can be shown to exist, should be more apparent in instances of recently disseminated tuberculosis affecting both lungs diffusely in a manner approximating closely the distribution of the pulmonary blood vessels.

DISSEMINATED HAEMATOGENOUS PULMONARY TUBERCULOSIS

Before discussing possible relations which may exist between morphological and roentgenographic appearances of miliary and nodular pul-

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[2] Presented at a session of the Post-Graduate Course in Tuberculosis at the Jewish General Hospital, Montreal, July 18, 1939.

monary tubercles and the rôle played by the components of the dual circulation in their development, the writer wishes to emphasize that the impressions to be presented are largely empirical. Postmortem examination of the viscera, after the disease has run its course, as a rule, gives little information as to the pathway taken by the infection. Few experimental studies deal with this problem. Of necessity, one has to rely on serial roentgenographic examinations and on clinical interpretations for information on the beginning of the disease. In the following discussion, the anatomical descriptions are taken from the authoritative studies of William Snow Miller (11), and on this background an attempt is made to correlate certain characteristics of haematogenous tuberculosis in the adult with the probable mode of development of the disease.

The lungs have a dual blood supply, one nutritive and the other engaged in gas interchange. Haematogenous infection and superinfection of these organs can occur by one or both these avenues. The lungs may be involved directly if tubercle bacilli escape from a caseous lymph node, usually one situated at the hilum, extend to one of the large lymph ducts, are conveyed to the left subclavian vein and superior vena cava to the right side of the heart and then invade the parenchyma by way of the pulmonary arteries. Bacilli may, of course, gain access to this channel anywhere along the route mentioned. Conceivably, a similar distribution of organisms may result if tubercle bacilli enter tributaries leading to the abdominal lymphatics or the inferior vena cava. The latter pathways, however, presuppose an antecedent localization of the disease in an abdominal organ as might occur in the course of systemic tuberculosis. It is improbable that these give rise to major pulmonary deposits as evidenced by the fact that wide-spread tuberculosis may exist in "surgical" forms of the disease without gross pulmonary involvement. Considering the extensive use of surgical procedures in the treatment of urogenital and osseous tuberculosis, it is surprising how few patients succumb to miliary tuberculosis or tuberculous meningitis as a direct result of operative interventions. The protracted nature of generalized haematogenous tuberculosis makes it occasionally appear as if an extrapulmonary nidus is the source of the pulmonary infection whereas, in reality, the reverse is much more often the case.

In addition to direct channels, by way of the pulmonary arteries, the lungs may be involved by the greater circulation as part of a systemic infection. This usually follows the discharge of tubercle bacilli from a caseous focus within or in close relation to a pulmonary vein, the bacilli

being disseminated from the left heart through the arterial system: the lungs are involved by way of the bronchial arteries. In a series of 181 cases of miliary tuberculosis, Hartwich (4) found the probable source of the infection in a pulmonary vein in 67 per cent and in the thoracic duct in 28 per cent. Other systemic veins were rarely involved. As might be expected, tuberculous meningitis occurred in two-thirds of the patients. Instances are on record of generalized haematogenous tuberculosis following rupture of a caseous focus into the thoracic aorta or one of the chambers of the heart. Such occurrences are rare. Under certain conditions, to be discussed later, tubercle bacilli may pass the capillary bed between the lesser and the greater circulations and a mixture of both forms of seeding may affect the lungs. A review of the many specific and nonspecific factors which enter into the pathogenesis of haematogenous tuberculosis is beyond the scope of the present discussion.

1. *Haematogenous pulmonary tuberculosis by way of the greater circulation:* The bronchial arteries arise from the thoracic aorta and often from other vessels as well: the upper thoracic intercostals, the internal mammary and the subclavian arteries. Two or three arteries accompany each bronchus and its subdivisions. They form a rich, anastomosing plexus about the bronchi, the lymphoid tissue and lymph nodes within the lung, the connective tissue septa and the pleura. The alveolar epithelium itself is nourished by terminal branches of the pulmonary artery. Circulatory transmission of tubercle bacilli by way of the bronchial arteries favors a uniform distribution of tubercles within the stroma of the lungs. Occasionally, one encounters on the X-ray film, as well as at necropsy, miliary tubercles of fairly even size symmetrically distributed in both organs from apex to base. The parenchyma between the individual tubercles appears uninvolved. The distribution of the tubercles does not seem related to the arborization of the tracheobronchial tree, each cubic segment of lung, measured grossly, containing a comparable number of tubercles. In the adult, the hilar lymph nodes are, as a rule, not enlarged unless the dissemination follows shortly a primary infection in the lungs. There are usually no other gross lesions within the lung; stigmata of a primary infection as well as inactive apical foci are usually present. In patients under sufficiently long periods of observation this type of haematogenous pulmonary tuberculosis is discovered in acute form, invariably as part of a systemic infection, often involving the meninges.

The following instance illustrates the condition. It is chosen primarily for the reason that the miliary tubercles are reproducible in a photograph. This is not possible in most instances of recent, acute disease.

Case 1: E. H., 24, admitted to the Montefiore Hospital April 21, 1927; died May 11, 1927. Three years previously the patient developed dysuria, haematuria and frequency. He was treated for a supposed cystitis and continued his studies. Toward the end of 1926 he became listless, lost weight and his urinary symptoms became worse. He entered a hospital in November where renal tuberculosis was discovered and a right nephrectomy done. A film of the chest taken before the operation is reported as showing no infiltrations in either lung. Following the operation, a fistulous tract remained. In the five months which elapsed between the time of operation and his entry to Montefiore Hospital, the patient noted increasing weakness and loss of 30 pounds in weight. The urinary symptoms were not as distressing. While waiting for a bed to become available at the Montefiore Hospital, he stayed in another institution. A film of the chest taken April 18, 1927 disclosed bilateral miliary tuberculosis.

Examination at the Montefiore Hospital revealed a haematogenous tuberculosis with milia of small size evenly distributed in both lungs (figure 1). The patient, from the day of admission, had symptoms and signs of tuberculous meningitis, verified by the finding of tubercle bacilli in the spinal fluid. The sputum did not contain the organism. He died three weeks later.

Necropsy, performed by Dr. D. Seecof, revealed a voluminous right lung, fixed to the chest by dense adhesions. On section, innumerable, grayish, firm, pin-point tubercles, all approximately of the same size, were present throughout the parenchyma. The left lung contained a puckered scar at the apex

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FIG. 1. E. H. April 22, 1927. Miliary tubercles symmetrically distributed in both lungs. Part of a generalized haematogenous tuberculosis, by way of the greater circulation, involving many organs including the meninges.

FIG. 2. E. H. Necropsy, May 11, 1927. Specimen of left lung, revealing miliary tubercles evenly dispersed in the parenchyma.

FIG. 3. H. P. December 4, 1937. Pneumothorax collapsing partly the right lung. No gross abnormalities in the left lung.

FIG. 4. H. P. June 18, 1938. Nodular tubercles now present in the collapsed and uncollapsed lungs. Accentuation of hilar shadows. Haematogenous tuberculosis by way of the lesser circulation without demonstrable extrapulmonary localizations.

FIG. 5. G. D. November 10, 1937. Exudative tuberculous infiltration in the left lower lobe. No gross abnormalities in the remainder of both lungs.

FIG. 6. G. D. June 28, 1938. Nodular tubercles now present in the collapsed and uncollapsed lungs. Haematogenous tuberculosis by way of the lesser circulation without demonstrable extrapulmonary localizations. X-ray films in early months of 1939, following reëxpansion of the left lung, revealed gradual clearing of infiltrations, leaving fine reticular changes in the parenchyma. A film taken July 19, 1939 showed complete clearing.

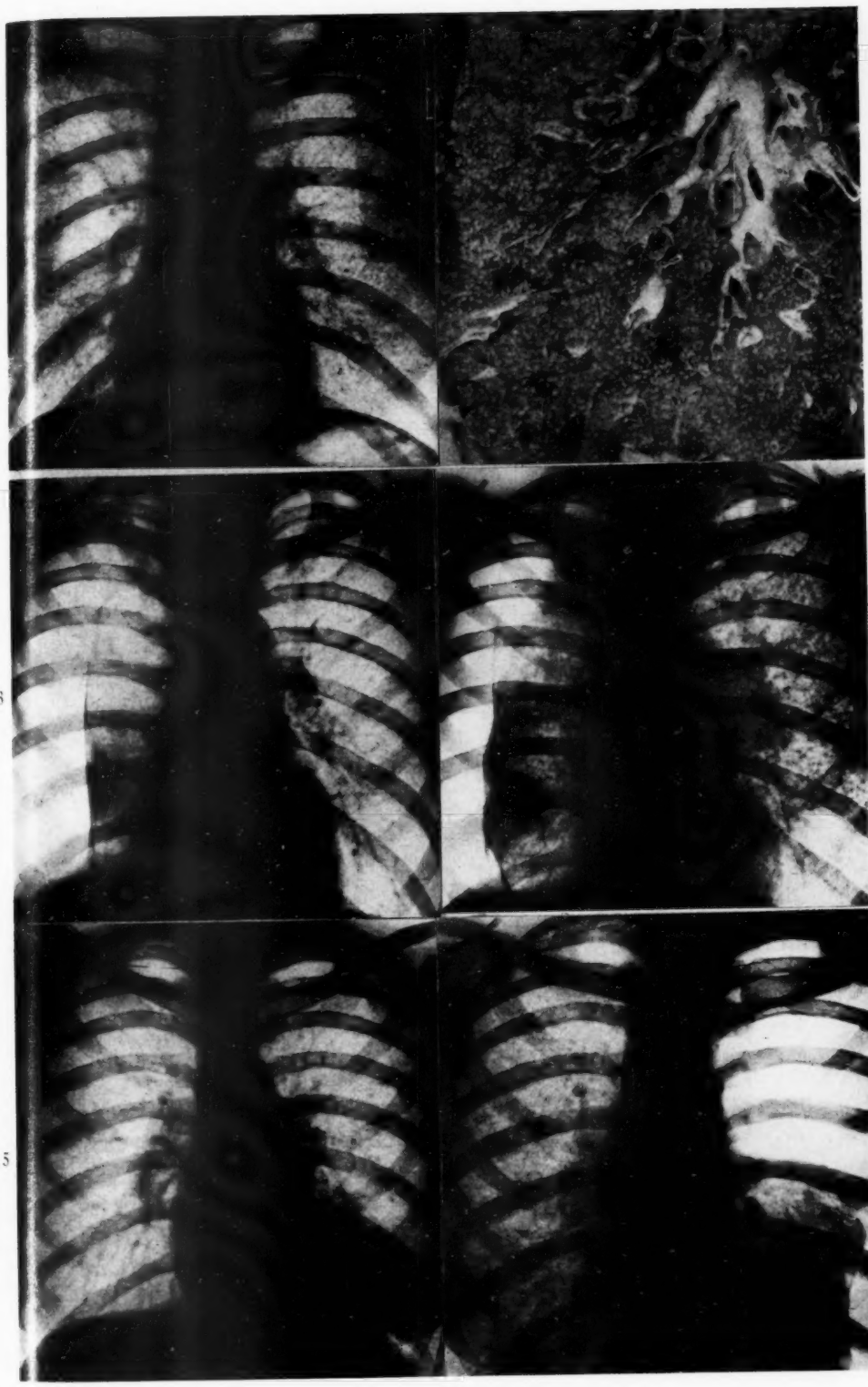

FIG. 1 FIG. 2

FIG. 3 FIG. 4

FIG. 5 FIG. 6

FIGS. 1–6

and on section revealed both lobes diffusely studded with tubercles (figure 2). The hilar lymph nodes were not enlarged. A large sinus was present at the right lumbar region, the tract covered by a thick layer of granulation tissue. The right kidney was absent; the left kidney contained scattered miliary tubercles. Small tubercles were present in the liver, spleen and adrenals. Larger areas of caseation were found in the prostate and urinary bladder. Section of the brain and pons revealed tuberculous meningitis.

An analogous type of distribution of tubercles in the lungs, but not quite as characteristic, is encountered occasionally in arrested forms of generalized haematogenous tuberculosis, the result of a single seeding. The individual tubercles are slightly larger and are either fibrosed or calcified. As a rule, they are not as numerous as in acute disease. Associated fibrous and emphysematous changes as well as recurring blood-stream infections alter the appearance of the initial dissemination and a distinctive picture of greater-circle tuberculosis, such as seen in recent disease, is not obtainable.

2. *Haematogenous tuberculosis by way of the lesser circulation:* The pulmonary arteries which carry blood to the alveoli for oxygenation are, in health, end arteries. They do not anastomose with the bronchial vessels, the capillary bed between the two systems maintaining functional rather than anatomical continuity. The transitional zone is a favorite site of tubercle formation. A single branch of the pulmonary artery follows the course and distribution of each bronchus, both being often encased in a single sheath. Each artery and companion bronchus subdivide in a tree-like manner, the former eventually breaking up into as many radicles as there are air sacs to be supplied. Haematogenous tuberculosis in the lungs arising by way of the lesser circulation, from an anatomical standpoint, favors the development of tubercles in the terminal air sacs and bronchioles. Like the configuration of the latter, the tubercles tend to appear in groups, are of larger than miliary size, somewhat irregular, presenting an acinous arrangement simulating mulberry or grape clusters about the terminal radicles of the bronchial tree. Because of the intimate association existing between the pulmonary arteries and the bronchial tree, the picture resembles superficially disseminated infiltrations such as occur during haemoptysis or following aspiration of fine deposits from apical cavities. For this reason, the condition is frequently confused with bronchogenous disease, as the term "bronchogenic miliary tuberculosis" would imply.

The degree of involvement varies in different parts of the lung. In

most instances the roentgenographic appearance is that of an uneven, soft or dense, nodular mottling in the upper parts of the lungs. At times, the involvement is greater in the middle and lower lobes. In patients with torpid disease, gradations in density between individual units register on the film as a fine or as a coarse fibrillar meshwork, such as one sees in lymphangitic carcinoma and which has been described as a "tuberculous reticular lymphangitis" (17). In adolescents and young adults, the hilar and paratracheal lymph nodes are usually visibly enlarged at some stage of the process, indicating recent participation of these structures. In the absence of gross cavitary disease (tubercle bacilli are often demonstrable in the sputum on careful examination) or of a history of haemorrhage or of considerable expectoration, this type of distribution of nodular tuberculosis, particularly when the disease in its earlier stages of development seems to be limited to the lungs, is suggestive of a haematogenous infection by way of the lesser circulation.

Lesser-circle tuberculosis, since it is so closely associated with the respiratory units of the lung, does not often appear in pure form and then only for a short time. On the whole, however, acinous tubercle formations tend to assume productive tendencies from the very beginning (1). Recognizable features of haematogenous, acinonodular tuberculosis are most apt to be encountered in young adults with sluggish disease of recent onset. The more acute the process, the sooner are distinguishing landmarks lost as the disease extends within bronchi and along lymphatics. In such cases early involvement of all channels of spread leading to bronchopneumonic and ulcerative tuberculosis, as well as to haematogenous dissemination elsewhere, is the rule.

The fact that the following two instances of pulmonary tuberculosis, by way of the lesser circulation, occurred in patients receiving pneumothorax treatment is a coincidence. One is more apt to discover developments of this nature in patients under close observation.

Case 2: H. P., 24, admitted to the Montefiore Hospital June 27, 1938. In the summer of 1934, the patient began to lose weight and to have fever. He improved with bed-rest but soon developed cough, expectoration, night sweats and blood-streaking. He was admitted to an institution in the fall where a film revealed a tuberculous process in the right lung. The sputum contained tubercle bacilli. Pneumothorax was induced in December, 1934. He entered the Montefiore Country Sanatorium where the treatment was maintained.

An effusion developed which was aspirated and replaced by air. The sputum no longer contained tubercle bacilli. In April, 1936 he was transferred to the Montefiore Clinic for the continuation of pneumothorax. An X-ray film of the chest taken in December, 1937 is reproduced (figure 3).

The patient felt well until March, 1938 when he began to experience headaches and a low-grade fever. A film of the chest showed no detectable changes in the pulmonary condition. The right lung was partly collapsed and a small effusion was present at the base. The left lung appeared clear. Later study of this film and comparison with previous and later films showed that there had occurred an accentuation of the shadows at the hilum as well as of the lung markings in the midparts of both lungs. The sputum did not contain tubercle bacilli on repeated examinations. An increase in the settling velocity of the blood was noted. For the following three months the patient continued to receive monthly refills of air. When he appeared for treatment on June 18, 1938, some haziness was made out in both lung fields on fluoroscopic examination. A film of the chest disclosed nodular tubercles occupying the major portion of the left lung as well as the partly collapsed right lung (figure 4). In spite of the striking change in the appearance of the lungs, the patient had few symptoms: no fever, no dyspnoea, very slight cough and little expectoration. On close questioning, after he entered the hospital, he admitted having experienced wheezing sensations in the chest on a number of occasions. Later films, after the collapsed lung had been allowed to reëxpand, showed no significant changes. The sputum continued to be free from tubercle bacilli. No tuberculous foci were found elsewhere on repeated examinations.

Case 3: G. D., 19, colored, admitted to the Chest Clinic of the Morrisania City Hospital November 9, 1938. The patient's illness began in the fall of 1937 with the onset of cough and expectoration. Late in October she developed fever and night sweats. At no time did she have blood-spitting. She was admitted to a city hospital a month later. Examination of the chest revealed an exudative tuberculous process in the left lower lobe. The right lung appeared clear (figure 5). Tubercle bacilli were found in the sputum. Pneumothorax was induced on the left side November 24, 1937 and a satisfactory collapse of the lung realized. The patient responded well to the treatment and tubercle bacilli could no longer be found in the sputum. She was transferred to another institution. An X-ray film of the chest taken about a month later revealed faint, irregular, nodular infiltrations radiating into the upper and midparts of the right lung. The left lung was well collapsed. Six months later, a comparison film showed these nodular infiltrations more distinctly, involving the entire right lung and the partly reëxpanded left lung (figure 6). Throughout this time the patient had no significant symptoms referable to the chest and no evidences of tuberculosis elsewhere

in the body. The patient's weight averaged 100 pounds; the sputum remained negative for tubercle bacilli; the sedimentation velocity of the blood was moderately accelerated. In the past few months the left lung has been allowed to become reinflated to its full volume. Latest films show a distinct tendency for the individual nodules to become indistinct and to become incorporated as a fine, fibrillar meshwork in the stroma of the lung. The disease appears to be in a process of healing by absorption and conversion into linear fibrous tissue (reticular lymphangitis).

The writer has been unable to find an illustration of lesser-circle tuberculosis more striking than one recently reported by Sweany (18). The contribution is concerned with possible routes of haematogenous infection and the factors of healing, latency and progression that enter into the evolution of pulmonary tuberculosis. Two instances are cited (cases 2 and 3) which are ideal examples of the subject under the present discussion.

Case 2 is particularly instructive. It deals with a boy with a family history of tuberculosis whose illness could be traced for about a year and a half. "It began with a swelling below the left ear, due to tuberculous lymph nodes. There was an ulcer of the left tonsil. The tuberculin test was positive. The X-ray revealed a questionable 'miliary tuberculosis' of the lungs. The blood revealed a mild anaemia, slight leucopenia and an unfavorable Schilling index. One month before death the sputum was found positive for tubercle bacilli. The postmortem revealed a primary tuberculosis in the left cervical region and at two places in the ileum with primary calcifications in the wall of the bowel and in the regional lymph nodes. There were huge ulcers in the bowel at these places showing that the primary lesions had remained open. The age type of all calcified lesions ranged from a four to six year type. There was an evenly distributed miliary tuberculosis in the lungs, more marked in the upper portions and decreasing in size in the lower parts. There were a very few small miliary tubercles in the spleen and liver, that were thought to be a terminal process. Amyloid was present in the liver and spleen." Sweany concludes that the instance described was that of a local miliary tuberculosis in the lungs due to a lymphogenous seeding by way of the thoracic duct. With his kind permission, a photograph (reduced) of the lung specimen is reproduced (figure 7).

Sweany emphasizes the difference in origin of the pulmonary involvement in the case just cited as compared to one (his case 3) in which the lungs were involved as part of a generalized dissemination. He does not draw attention to what seem to be equally distinct differences in the

gross appearance of the disease, as shown in the illustrations. A comparison of the X-ray films and of the photographs of the lung specimens reveals that in the instance of generalized haematogenous tuberculosis the tubercles are of miliary size and are evenly distributed in both lungs while in the instance of haematogenous seeding by way of the thoracic duct and the pulmonary arteries the lungs reveal larger, uneven tubercle formations of an acinonodular character. Since the duration of the disease was judged to have been approximately the same in both patients, one a boy of eleven and the other a boy of six, it is plausible to assume that the different pathways taken by the blood-stream infection were responsible for the variations noted in the topographic distribution of the disease.

A unique experience, recently reported by Lemierre and Ameuille (7), illustrates graphically the subject under discussion. It relates to a successful attempt at suicide by means of self-administered intravenous injection of a suspension of virulent, human tubercle bacilli.

The patient, a physician aged 29, with a family history of tuberculosis was under the apprehension that he, too, was suffering from the disease. A definite diagnosis of tuberculosis, however, was never made. Several months previously his tuberculin reaction was positive. He had been working in a tuberculosis institution for some time. On April 17, 1932 he injected into his left cubital vein 2 cc. of a suspension of human tubercle bacilli, containing about 1 mg. of organisms per cc. The material had been obtained from a culture

FIG. 7. Fig. 1 of case 2, reported by H. C. Sweany and reproduced by permission. Acinonodular tuberculosis in groupings, more extensive in the right upper lobe. According to Sweany, an example of lymphohaematogenous tuberculosis by way of the thoracic duct and the pulmonary arteries.

FIG. 8. G. P. November 1, 1932. Acinonodular tuberculosis concentrated mainly in the midlungs which, on section, assumed a mulberry arrangement along the distribution of the bronchi. An instance of lesser-circle tuberculosis involving also the greater circulation, as evidenced by the presence of a circumscribed tuberculous abscess in the left kidney and two ulcers in the urinary bladder. Necropsy, December 12, 1932.

FIG. 9. B. F. August 4, 1927. Large cavity in the right upper lobe. Exudative infiltrations in the remainder of both lungs. Pott's disease. Papulonecrotic tuberculids in skin.

FIG. 10. B. F. February 8, 1937. Ten years later. Fibrosis in right upper lobe, remains of healed cavity. Numerous calcific foci in other lobes.

FIG. 11. T. L. February 29, 1926. Marked fibrosis and bronchiectasis of right upper lobe. Emphysema of left lung. Note heteroplastic bone formation, indicated by arrow.

FIG. 12. T. L. Necropsy, September 11, 1926. Specimen of right upper lobe. Intense fibrosis and bronchiectasis. Miliary tubercles in remainder of both lungs. In addition, there were found numerous calcified tubercles over left visceral pleura and a terminal miliary tuberculosis.

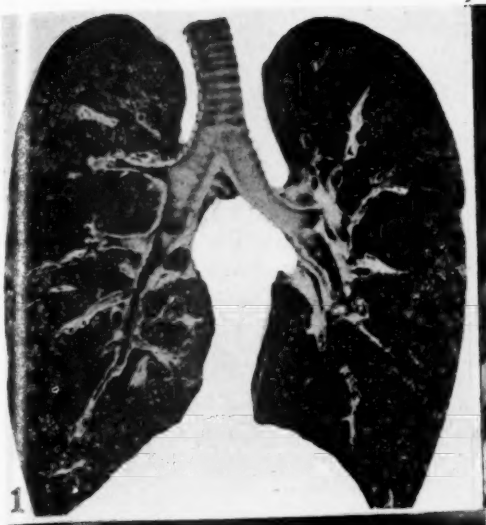

Fig. 7

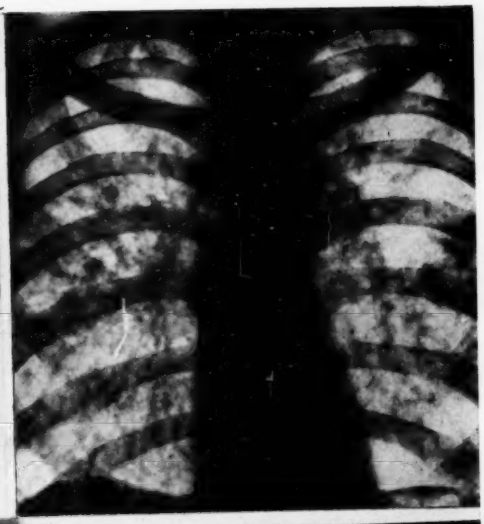

Fig. 8

Fig. 9

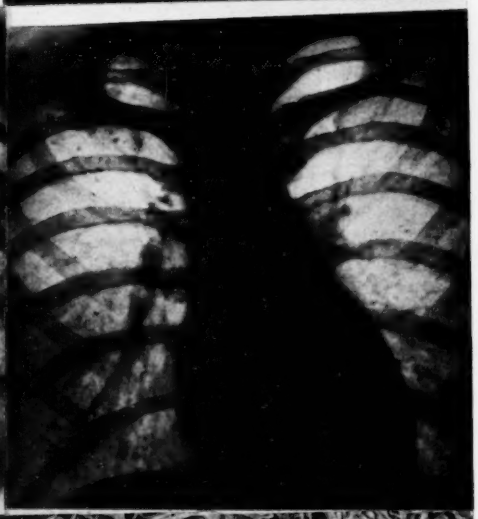

Fig. 10

Fig. 11

Fig. 12

Figs. 7–12

of a tuberculous pleural effusion. Two days later he experienced a febrile attack associated with malaise and chill. Being at first unaware of the true state of events, his physicians examined him carefully for signs of sepsis. Blood cultures and other tests proved negative. Later, the history was revealed to them. On the 26th day of April, nine days after the inoculation, an X-ray film of the chest showed what were considered no significant abnormalities in either lung. On May 19, thirty-two days after the inoculation, a comparison film disclosed small tubercles in both lungs. The tubercles were better visualized on a film taken July 2, two and a half months after the inoculation. They appeared most numerous in the middle and lower parts of both lungs. The hilum markings were not accentuated. The clinical course of the disease was characterized by a paucity of physical findings. He had high fever, splenic enlargement which could be ascribed to the toxaemia, a leucopenia and a secondary anaemia. At no time were extrapulmonary foci discovered. Repeated examinations of the sputum, urine and blood by direct and animal inoculations failed to reveal tubercle bacilli. Symptoms and neurological signs of tuberculous meningitis appeared about the 10th of July and death occurred on the 14th of July, approximately three months from the time of the inoculation.

The instance cited is an excellent example of initially lesser-circle tuberculosis as far as can be judged from the data presented, which are sufficiently detailed to give a good picture of what happened. Following the injection into the cubital vein, the tubercle bacilli seeded the lungs by way of the pulmonary arteries. There were no tuberculous foci in any other organs. From the illustrations accompanying the case report, it appears that the topography of the nodular tubercles in the lower parts of both lungs is in keeping with a haematogenous infection by way of the lesser circulation. The significance of the tuberculous meningitis, which developed late in the disease, indicating invasion of the greater circulation, will be discussed shortly.

3. *Later developments in haematogenous pulmonary tuberculosis:* It is the rare case in which one can attempt to correlate the channel of spread with the morphological appearance of the disease, as revealed by the clinical and X-ray findings. Even when the disease pursues a torpid course and remains in "closed" form without gross communication with bronchial channels there is a tendency for haematogenous tuberculosis to become generalized and to assume an undulant course as recurring blood-stream disseminations of tubercle bacilli infect and reinfect the various organs of the body. Ulceration into bronchial channels and direct spread in the tissues add that much more to the difficulty of tracing

the mode of onset of the disease. But there is some evidence at hand that even these transformations, insofar as they pertain to the blood supply of the lungs, are also related in part to altered anatomical conditions which manifest themselves with establishment of disease in the lungs.

According to the researches of Ghoreyeb and Karsner (2), Wood, Crever and Miller (20), and Mathes, Holman and Reichert (9), inflammatory changes in the lungs, and conceivably in limited parts of a lung, induce alterations in the relation existing in the dual circulation. An additional supply of blood is brought to nourish the parenchyma: the bronchial arteries become dilated, their ramifications more numerous, and the capillaries between the bronchial and pulmonary arteries rapidly increase in size in response to greater functional demands. With the pulmonary arteries more actively engaged in oxidative processes, there is soon established a collateral circulation between the two systems. Removal of the physiological screen between the lesser and greater circulations allows passage of tubercle bacilli and repeated superinfections of the lungs by either and both circulatory routes. Under these conditions extrapulmonary foci may follow lesser-circle tuberculosis. If the greater circulation is involved early in the course of the disease, as is often the case, the clinical picture is that of a generalized miliary tuberculosis and the nature of the initial dissemination is not recognized.

Case 4: G. P., 20, admitted to the Montefiore Hospital October 21, 1932; died December 12, 1932. At the age of fifteen, the boy began to lose his appetite and to tire easily. Occasionally he had night sweats and intermittent dull chest pains but no cough or expectoration. After a rest in the country, he improved and returned to school. A year later the symptoms recurred. The condition was diagnosed as tuberculosis and the boy entered a city institution. Sputum examinations at this time failed to reveal tubercle bacilli. He then spent a year at the Montefiore Country Sanatorium. Here, films of the chest revealed nodular tubercles involving chiefly the upper lobes. He soon developed anorexia, abdominal cramps and diarrhoea. He was transferred to the Montefiore Hospital. A film revealed the nodular tuberculous process now more accentuated in the midparts of both lungs (figure 8). The patient's complaints were referable mainly to the abdomen and were ascribed to the presence of intestinal tuberculosis. He died six weeks after his transfer.

Postmortem examination, performed by Dr. C. Spark, revealed both lungs studded with acinonodular tubercles arranged along the distribution of the bronchi. The tubercles assumed a mulberry arrangement and were most numerous in the lower portions of the upper lobes and in the lower lobes.

They showed central fibrosis and anthracosis. There were no areas of pneumonia and the intervening parenchyma was emphysematous. A small cavity was present in the left upper lobe. In addition, the intestines revealed large denuded areas of tuberculous ulceration. Superficial ulcerations were present in the epiglottis and vocal cords. The left kidney had a circumscribed, tuberculous abscess and there were two ulcers in the urinary bladder. Miliary tubercles were present in the liver and the spleen.

Haematogenous pulmonary tuberculosis, regardless of the mode of onset, evolves in its later stages much in the same manner. The tuberculous process may heal, may remain latent or may progress to bronchopneumonic and cavitary changes. There are several points of difference in the early stages of lesser-circle as compared to greater-circle tuberculosis involving the lungs which come to the foreground when one reviews a large number of cases. Providing perifocal inflammatory reactions are at a minimum, tubercles arising by way of the bronchial arteries are apt to retain their identity for longer periods than is the case with tubercles arising by way of the pulmonary arteries. In the former, cavities when they occur are of small size, isolated and not in open communication with bronchi until late in the disease. As a result, tubercle bacilli are rarely found in the sputum at this stage. The contrary is true in instances of lesser-circle tuberculosis. In the latter, cavities appear earlier and are often multiple; tubercle bacilli, although sparse in number, are usually demonstrable in the sputum unless the disease is in a process of healing. As a corollary to these observations, symptoms and physical findings relating to the lung involvement are apt to be more prominent in this type of haematogenous tuberculosis. These vary with the character of the process and, as is true of tuberculosis in general, rarely equal the extent of the disease as seen on the X-ray film.

Noteworthy, too, is the fact that in instances of haematogenous pulmonary tuberculosis, by way of the greater circulation, extrapulmonary tuberculous localizations are discovered coincidentally with and occasionally prior to the pulmonary involvement. Haematogenous pulmonary tuberculosis, by way of the lesser circulation, precedes extrapulmonary localizations. Quite often the disease remains for a long time limited to the lungs, as far as can be judged clinically. Typical instances which bring out these characteistics with respect to greater-circle tuberculosis have been detailed in a previous paper (16).

In the following discussion, a few examples of haematogenous pulmonary tuberculosis will be presented to illustrate the several modes

of evolution of the disease. No attempt will be made to speculate on the nature of the original infection from a genetic standpoint. In most of the patients the disease had been present for a number of years.

Evidences of healing of disseminated haematogenous pulmonary tuberculosis may be discovered in one of three major forms. (*1*) Occasionally, as illustrated by case 3, there are left in the lungs fine, linear strands which are not distinguishable from surrounding structures unless earlier X-ray films are available. Pagel and Henke (13) describe minute, emphysematous vesicles, an accompaniment of this type of healing. Clinically, there is a reduction in the vital capacity and, occasionally, dyspnoea simulating asthma. (*2*) Multiple, calcified foci are, at times, the end result of haematogenous pulmonary infiltrations. These often have a predilection for the subpleural parts of the lungs where they appear as flat, ovoid nodules. Although the core of these nodules is calcified and the periphery composed of concentric layers of fibrous tissue, caseous excrescences may be present within adjacent lung substance and the disease may later become active in these locations. This state of affairs was recently illustrated on histological examination of sections of a lung of a patient with subpleural calcifications who died from an intercurrent subacute bacterial endocarditis. (*3*) In still others, there develops intense fibrous scarring of a diffuse or a localized nature, often associated with bronchiectasis and invariably with some degree of emphysema.

The following two instances illustrate the latter forms of metamorphosis of haematogenous pulmonary tuberculosis.

Case 5: B. F., 20, admitted to the Montefiore Country Sanatorium August 3, 1927 with a history of onset dating to December, 1925 when she experienced pain in the lower back. She continued at school but soon developed anorexia, loss of weight and weakness. In February, 1927 she began to cough and several months later tuberculosis was discovered by X-ray and sputum examinations. At the Sanatorium an X-ray film of the chest revealed numerous infiltrations disseminated in both lungs with a cavity in the right upper lobe (figure 9). Tubercle bacilli were present in the sputum. She remained at the Sanatorium until December, 1928 and was transferred to the Montefiore Hospital for treatment of a mass at the right thigh. This mass was found to be a psoas abscess secondary to tuberculosis of the fourth and fifth lumbar vertebrae. She remained at bed-rest for the following two years. In 1929, papulonecrotic tuberculids were discovered in the skin. For a time, thereafter, she was under observation in the Tuberculosis Clinic. Films of the

chest showed a gradual clearing of the process in both lungs, the cavity becoming converted into a fibrotic scar and the exudative deposits undergoing calcific changes. The healing was complete in 1931. For the past few years she has been working as a nurse at the Sanatorium and has enjoyed good health. A film taken in 1937 is reproduced to show the condition of the lungs after an interval of ten years (figure 10).

Fibroid tuberculosis with secondary bronchiectasis and emphysema does not present, offhand, any of the stigmata commonly associated with haematogenous disease. Yet, there is reason to believe that such is the case in many instances. The disease is commonly discovered in advanced age. Its chronic course is occasionally interrupted by acute episodes which may not be related to the tuberculosis directly. As a result of the bronchial changes, pleuritis and emphysema, there are usually obtainable physical signs on percussion and auscultation. The symptoms are characterized by moderate expectoration, unless the bronchiectasis is suppurative, in which case the expectoration may be profuse and, at times, bloody. The temperature is often subnormal. Tubercle bacilli are not present in abundance in the sputum and are often absent. The following instance is illustrative of the condition.

Case 6: T. L., 62, admitted to the Montefiore Hospital October 10, 1924; died September 11, 1926. Ten years previously the patient developed a slight cough, pain in the left chest and weakness. Tuberculosis was diagnosed and he entered the Montefiore Country Sanatorium for a short stay. This he repeated on several occasions. In 1923, he developed a fistula-in-ano. He was admitted to the Montefiore Hospital in October, 1924, where physical and X-ray examinations revealed dense infiltrative disease in the right upper lobe and small rarefactions suggestive of saccular bronchiectasis. The left lung appeared clear (figure 11). Repeated examinations of the sputum failed to reveal tubercle bacilli. After a short interval, spent in the Sanatorium, he was readmitted with fever to 104°F. and signs of acute miliary tuberculosis. He died shortly thereafter. Postmortem examination, performed by Dr. D. Seecof, revealed fibroid tuberculosis with bronchiectasis of the right upper lobe; fibrous pleuritis and heteroplastic bone formation and chronic adhesive pericarditis (figure 12). Numerous, small, calcified tubercles were present over the left visceral pleura, the remains of an ancient haematogenous seeding. A terminal miliary tuberculosis involved the rest of both lungs, the spleen, kidneys, prostate and thyroid.

When the disease pursues a torpid course, the involvement is apt to be most pronounced in the midparts of both lungs, the organs presenting

an appearance commonly described as "peribronchial" tuberculosis. As mentioned previously, the lymphatics probably play a rôle in concentrating the infection along the perivascular and peribronchial channels. The lymphatics become involved coincident with or shortly after the haematogenous tubercles become established in the subpleural layers of the lungs. Retrograde extension from mediastinal lymph nodes occurs under exceptional conditions.

Case 7: A. G., 54, admitted to the Montefiore Hospital May 23, 1928; died June 27, 1928. The patient, an employee of the Hospital, was told that he had chronic bronchitis for a number of years. He felt fairly well until five years prior to his admission as a patient when he noted loss of weight, increased cough and expectoration and occasionally night sweats. A film of the chest revealed nodular infiltrations occupying chiefly the middle two-thirds of both lungs (figure 13). His course was rapidly downhill and he died a month later.

Postmortem examination, performed by Dr. D. Perla, revealed all the lobes of the lungs studded by irregular, mulberry-shaped, sharply defined nodules following the course of the bronchi. Many of the nodules contained anthracotic pigment and were fibrotic. The periphery of many was caseous. Several small areas of cavitation were noted in the left upper lobe. There were terminal miliary tubercles in the spleen and liver.

In instances of progressive disease, the tuberculous foci in the lung do not retain their individual identity for any length of time. There is early ulceration of bronchi resulting in regional spread of the disease. At times, the disease is confined to the upper lobes, the result of a limited haematogenous seeding. Although this occurs more often in the post-primary period, late exacerbation of the disease may also produce a similar picture. Haematogenous upper lobe disease need not be the end result of a more wide-spread process in the lungs; the other lobes may have escaped tuberculous changes from the beginning. At times, numerous cavities develop from apex to base. Laryngeal and intestinal tuberculosis are not uncommon and a wide-spread haematogenous dissemination is a frequent terminal event. In such instances, the symptomatology is that commonly associated with ulcerative tuberculosis.

Case 8: H. M., 19, admitted to Montefiore Hospital March 24, 1931; transferred to the Montefiore Country Sanatorium April 23, 1931; readmitted to the hospital January 4, 1933; died February 6, 1933. About eight months prior to his first admission the patient began to cough and expectorate. He lost weight and became weak. Examination revealed both lungs seeded with

small, nodular infiltrations, most marked in the upper lobes. The sputum contained tubercle bacilli. He was transferred to the Sanatorium where the disease steadily progressed. Many cavities soon developed varying in size from a half inch to an inch and a half in diameter. The cavities appeared thin-walled, a number containing small collections of fluid at the bases. There appeared to be little consolidation of the adjacent lung tissue (figure 14). Shortly thereafter the patient developed symptoms of laryngeal and intestinal tuberculosis and died.

As noted in the last film, taken about two weeks before exitus, at necropsy, performed by Dr. S. Boharas, all the lobes were occupied by numerous intercommunicating, thin-walled cavities which were traversed by thrombosed branches of the pulmonary artery and vein. There was surrounding haemorrhagic oedema of the lung tissue and scattered caseous tubercles. Recent superficial ulcers were present in the pharynx, larynx and intestines.

CIRCUMSCRIBED FORMS AND TRANSITIONAL STAGES OF HAEMATOGENOUS PULMONARY TUBERCULOSIS

In the development of tuberculosis of a kidney or a joint, it is taken for granted that an active nidus is or was present elsewhere in the body from which tubercle bacilli were carried by the blood-stream to the particular organ involved. The lungs, supplied by external as well as internal communications, have for years presented a problem with respect to the mode of onset of pulmonary tuberculosis. Of late, it is becoming increasingly more evident that the first infection with the tubercle bacillus is acquired by inhalation of small numbers of bacilli resulting in the formation of a primary complex, the features of which are quite characteristic. Clinical tuberculosis, on the other hand, arises in the majority of individuals from endogenous superinfection of the lung

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FIG. 13. A. G. May 21, 1928. Bilateral acinonodular tuberculosis. The lungs, on section, revealed irregular, mulberry-shaped, sharply defined nodules following the course of the bronchi. Several small areas of cavitation were present in the left upper lobe. Necropsy, June 27, 1928.

FIG. 14. H. M. January 16, 1933. Numerous, intercommunicating, thin-walled cavities in both lungs. Necropsy, February 6, 1933, revealed, in addition, ulcers in the pharynx, larynx and intestines.

FIG. 15. L. R. March 27, 1929. Nodular, calcific infiltrations in both upper lobes, chiefly the left.

FIG. 16. L. R. September 24, 1929. Activation of the disease with bronchopneumonic spread in the left lower lobe and the right midlung.

FIG. 17. I. C. April 24, 1934. Thickened pleura on left, the remains of a tuberculous effusion. Large, round cavity in the left upper lobe which appeared eighteen months after the pleuritis. Tubercle bacilli present in sputum.

FIG. 18. I. C. June, 1936. Complete disappearance of cavity. Tubercle bacilli not demonstrable in sputum.

FIG. 13

FIG. 14

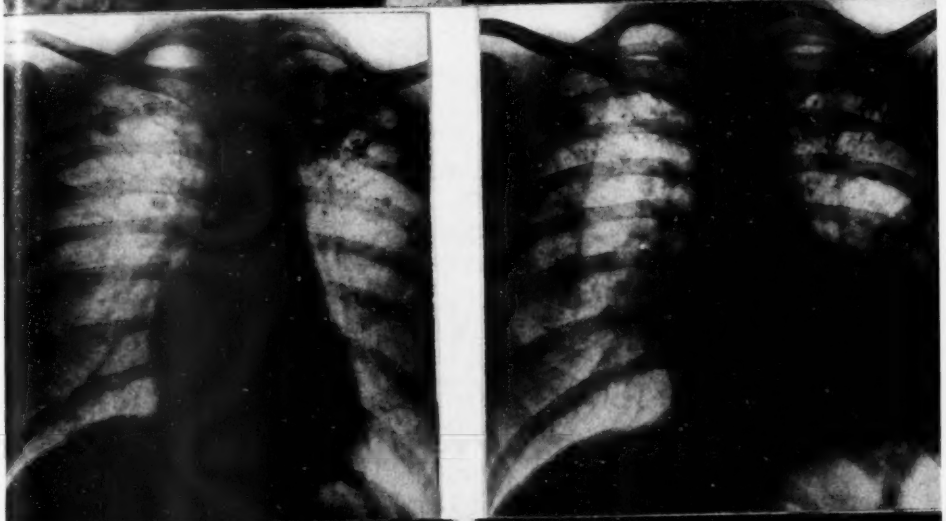

FIG. 15

FIG. 16

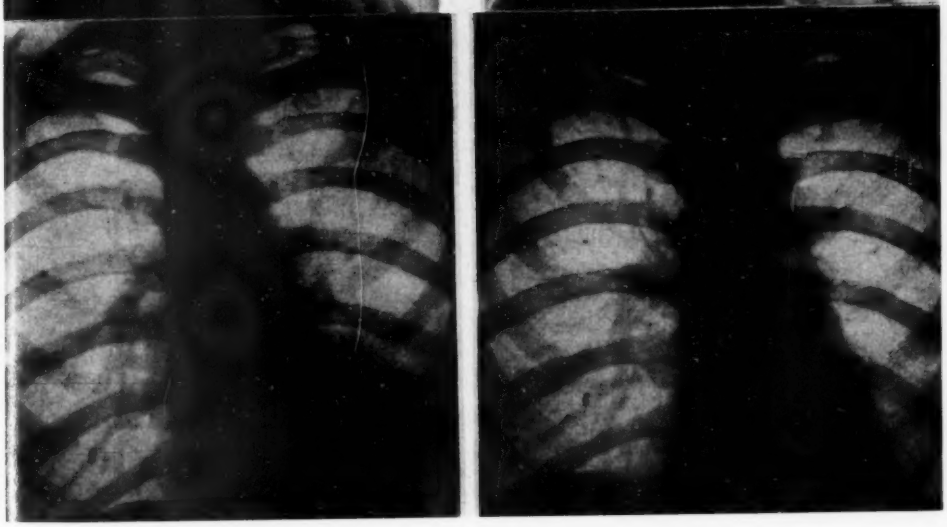

FIG. 17

FIG. 18

FIGS. 13–18

or from activation of foci established previously by such seeding. A clear distinction, however, between endogenously and exogenously acquired tuberculosis cannot be made in any given instance for the reason that there are few dependable criteria to distinguish the two. Furthermore, once the disease establishes itself in the lungs, it spreads by all available channels and the original pathway by which the tubercle bacilli gained access cannot be traced. In instances of systemic tuberculosis, the endogenous (haematogenous) origin of the lung involvement finds support in a bilateral, more or less uniform distribution of small infiltrations, the presence of the tuberculosis in deep-seated organs, a tendency for the disease to spread by blood channels, and an absence of tubercle bacilli in the sputum before the occurrence of bronchial ulceration. Some evidence was presented previously to indicate that disseminated, nodular and miliary tubercles in the lungs may be of haematogenous origin even in the absence of extrathoracic tuberculous foci. But when the infection in the lung is of a limited nature, few or none of the indices of haematogenous tuberculosis may be present; nevertheless, one may have reason to suspect that one is dealing with a disease of this character.

As stated previously, haematogenous pulmonary tuberculosis, whether arising by way of the greater or the lesser circulation, is only occasionally encountered in pure form and then only in the initial stages of the disease. Sooner or later bronchial ulceration takes place and one is no longer dealing with a haematogenous disease but with a combined haematogenous-bronchogenous disease, involving larynx, intestines and other organs. Knowledge of the many forms in which tuberculosis may appear in the lungs is necessary for a complete understanding of the life-history of the disease. To round out the discussion, two instances will be cited to illustrate some of the features of circumscribed haematogenous pulmonary foci which have evolved into bronchopneumonic and cavitary tuberculosis.

1. *Fibrocalcific infiltrations—bronchopneumonic spread:* Fibrocalcific infiltrations in the apical parts of the upper lobes are, as a rule, of haematogenous origin which often date to the period following the primary infection. Their symmetrical distribution, the occasional coexistence of extrapulmonary disease, so-called "surgical" tuberculosis, as well as certain morphological characteristics support this view. In most instances, foci of this nature, particularly when limited to the apical regions, are of an abortive nature and do not evolve into progressive tuberculosis. Occasionally, activation takes place leading to disease in

subapical parts of the lung. The extent of the calcifications in the following patient is much greater than that usually seen. The reader is referred to a study by Pinner (14) describing similar forms of nonmiliary haematogenous tuberculosis.

Case 9: L. R., 28, admitted to the Montefiore Hospital September 21, 1929; died December 21, 1929. In February, 1927, the patient was admitted to a general hospital complaining of raising bloody sputum and cough. A film of the chest disclosed "numerous small, calcific, nodular infiltrations in both apical regions." The sputum contained tubercle bacilli. She entered a sanatorium and remained there for one year. She gained 23 pounds in weight and was discharged with apparently arrested disease. She worked part-time under medical supervision. A routine film of the chest taken at the Montefiore Hospital March 27, 1929 revealed findings analagous to those noted two years previously (figure 15). Shortly after the film was taken she began to cough, expectorate bloody sputum and to have fever. She soon developed hoarseness and pain on swallowing. On admission to the Montefiore Hospital, in September, 1929, a comparison film of the chest disclosed, in addition to the calcific tubercles in the upper lobes, a fairly extensive consolidation in the left lower lobe. A small area of consolidation was noted also on the right side extending from the hilum (figure 16). The sputum contained tubercle bacilli. At the hospital she had high fever and other symptoms of progressive disease. She died three months after admission. A postmortem examination was not made.

2. *Pleurisy with effusion—subapical cavity:* Mention was made on several occasions of the frequent involvement of the serous membranes in the course of haematogenous tuberculosis. Particularly frequent is tuberculosis of the pleura with or without demonstrable effusion. Tuberculous pleurisy may be present as part of a generalized haematogenous disease or as part of a limited pulmonary disease. As a rule, the pleural effusion appears on the side of the parenchymal lesion when the disease is unilateral. Quite often nodular infiltrations are present, evenly distributed in both upper lobes. At times, the discovery of the pleural effusion antedates that of the parenchyal involvement by months or years. In others, a parenchymal lesion is never detected clinically. Occasionally one encounters patients with effusions recurring on the same side or effusions in both pleural cavities, the latter usually appearing successively. The writer has, at present, three such instances under observation. Were it not for the obliteration of the pleural space, which usually follows absorption of the exudate, effusions would be found to recur much more often.

The following patient is an example of pleurisy with effusion followed by subapical cavitation and spontaneous healing of the latter. The origin of subapical tuberculosis has received considerable attention. This case demonstrates a probably haematogenous development.

Case 10: I. C., 21. In 1932 the patient developed a pleurisy with effusion on the left side which occupied the lower part of the pleural cavity. The fluid was aspirated several times. She had fever and loss of weight. Subsequent films of the chest showed no signs of parenchymal involvement. After resting at home for five months, she returned to work. After working as a stenographer for about eighteen months, symptoms returned. At this time (1934) an area of infiltration was found in the left upper lobe. She had slight cough and expectoration and on several occasions spat up blood. Tubercle bacilli were not found in the sputum until April, 1934 when a film of the chest revealed a fairly large, isolated, subapical cavity in the left upper lobe (figure 17). The patient then spent some time in a hospital and later rested at home. No collapse measures were attempted. Serial films showed a gradual diminution in the size of the cavity and by June, 1936 the cavity was no longer visible (figure 18). At present, she weighs 120 pounds, has few symptoms referable to the chest and no tubercle bacilli in the sputum. The settling velocity of the blood is still moderately accelerated. She continues to do well and has returned to work.

DISCUSSION

The purpose of the foregoing presentation is to direct attention to and to stimulate further study of the rôle which the dual circulation plays in giving rise to clinically and roentgenographically somewhat dissimilar forms of haematogenous pulmonary tuberculosis. From our observations it would seem that dissemination by way of the bronchial arteries favors the formation of small, evenly dispersed tubercles, while dissemination by way of the pulmonary arteries favors the formation of tubercles of larger size in acinous groupings. Radiopaque substances injected into the lungs by either the bronchial or the pulmonary arteries provide an anatomical counterpart for the two chief forms of haematogenous tuberculosis described in these pages (9). Obviously, the many morphological manifestations which the disease assumes in the lungs and in other organs preclude an arbitrary division of haematogenous tuberculosis into that of lesser- and greater-circle origin. As mentioned previously, not only the blood-stream but all avenues of infection are involved, at an early date, and the origin of the disease is obscured in most instances.

Physicians who have studied the question of haematogenous pul-

monary tuberculosis have not given much attention to anatomical differences in explaining certain features of the disease. They have concerned themselves chiefly with morbid pathological changes. In analyzing the several forms of haematogenous pulmonary tuberculosis, Gräff and Küpferle (3) and Nicol (12) draw a distinction between the interstitial and the acinar miliary tubercle, each of which may assume exudative or productive tendencies. In their opinion, the acinar tubercle is the result of excretion of tubercle bacilli and their toxins into the alveolar spaces of the lung, that is, a further developmental stage of the interstitial tubercle. They do not consider the additional possibility that the channel by which the bacilli initially invade the lungs may be a factor in determining the mode of development of the tubercles. The qualifying *additional* is used advisedly. There are so many elements involved, even a seasonal one, that no single factor can be given exclusive prominence in explaining the genesis of haematogenous tuberculosis. Topography is stressed in this paper simply because it is of particular interest from a clinical and roentgenographic standpoint.

It is claimed that the histopathological reaction of the tubercle, whether it be exudative, productive or a mixture of both, is not related to its site of origin (5). Most authorities share this view although a few maintain that the acinous tubercle is more likely to undergo productive changes. But insofar as the topographic and gross appearance of disseminated haematogenous tuberculosis is concerned, it is conceivable that when tubercle bacilli reach the lungs, either by the pulmonary or the bronchial arteries, the resulting morphological changes may occasionally assume roentgenographic patterns such as have been described. Although chronicity influences greatly the topographic appearance of the disease, certain characteristics of lesser-circle as compared to greater-circle tuberculosis crop up repeatedly which serve to focus attention to the channel of the bacillary dissemination regardless of the nature of the disease. For example, Pagel and Henke (13) cite an instance of primary intestinal tuberculosis with abscess formation in which fresh tubercles situated in the alveolar portions of the lungs showed a productive tendency. This experience brings to mind the case of lesser-circle tuberculosis of Sweany described previously.

There is little to be found in the literature on the subject of lesser-circle as compared to greater-circle tuberculosis of the lungs from a clinical and roentgenographic standpoint. Many mention the fact that tubercles may arise in the lungs as a result of seeding by either or both the bronchial and pulmonary arteries without attempting to find dis-

tinguishing characteristics. Two observations on asphyxic forms of haematogenous pulmonary tuberculosis prompted Letulle and Bezançon (8) to differentiate a haematogenous disease characterized by small islands of "caseous alveolitis" from the conventional gray granulation typifying the miliary tubercle. On the basis of their observations, Jaquerod (6), in his book *The Natural Processes of Healing in Pulmonary Tuberculosis*, includes two representative X-rays of lesser-circle and greater-circle pulmonary tuberculosis.

The clinical studies that have been published on haematogenous tuberculosis lend support to the belief that occasionally one can hazard a genetic differentiation of the pulmonary disease. More important, however, than the diagnosis *per se* is the impetus this gives to qualitative study of the condition. Ulrici (19), an early contributor to the clinical and roentgenographic aspects of haematogenous tuberculosis, analyzes his material according to whether or not the disease was limited to the lungs or was part of a generalized process. His case reports of disseminated tuberculosis confined to the lungs typify many of the characteristics of lesser-circle tuberculosis mentioned previously. One is struck with certain features in the cases reported by Pinner (14) which lead one to suspect that in many of his patients with roentgen appearances of "large type foci" and "heavy hila" the disease was of lesser-circle origin. Most of the patients cited had torpid disease. Some had tubercle bacilli in the sputum. Extrapulmonary tuberculous complications appeared late or were absent. Zavod's (21) report includes several instances of acute, haematogenous disease which fall in the group of lesser-circle origin on the basis of the criteria mentioned. It is noteworthy that the recent contribution of Miller (10) on pulmonary tuberculosis in the adult describes in great detail various forms of the disease on the basis of their circulatory mode of origin.

As the disease progresses in the lungs, distinctions between haematogenous and bronchogenous tuberculosis become a matter of academic interest. The clinical course bears no relation to the genetic character of the tuberculous process. The acuteness or the chronicity of symptoms and the outcome in the individual instance depend on humoral factors which cannot be correlated with the manner of development of the disease. Although there is a tendency for haematogenous disseminations to recur, the prognosis, by and large, depends on whether or not the tuberculous foci are encapsulated or are in open communication with bronchial channels. The presence or absence of cavities secreting tubercle bacilli and the nature of these cavities (location, age, number,

size, etc.) are of much more significance from the point of view of prognosis and treatment than is their origin.

The writer is greatly indebted to Dr. Max Pinner, Chief of the Division of Pulmonary Diseases, Montefiore Hospital, for his help in the preparation of this and the previous paper.

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BASAL TUBERCULOSIS[1]

LAUREN F. BUSBY

For over forty years after Kidd (1), in 1886, and Fowler (2), in 1888, suggested that tuberculosis might attack the lower lobes of the lung before involving the upper lobes, little or nothing was added to our knowledge of basal tuberculosis. Before 1923 it was believed generally that pulmonary tuberculosis localized first in the apices and that basal lesions were extremely rare or occurred as terminal phenomena. In 1923, evidence was presented by Wessler (3), as well as by Assmann (4), to show that clinically active tuberculosis appeared frequently in the area below the clavicles. Later studies have shown that, although less frequent, the disease may appear first in the lower half of the lung.

The onset, in this type of tuberculosis, tends to be acute, occasionally very acute (Ross (5)), it may simulate pneumonia (Dunham and Norton (6)), but occasionally it may exist for years without noticeable impairment of health (Pindell (7)). The commonest symptom is cough (Colton (8), Lathrop and Lyman (9)) with more or less expectoration and, finally, haemoptysis (8). The symptoms may be the same as those of upper lobe tuberculosis (Hamilton and Fredd (10)), or they may be not unlike those of nonspecific pulmonary basal infection (Gordon and Charr (11)). The incidence of lower lobe disease is variously estimated as rare (DuFault (12), Reisner (13)), 0.0034 per cent (8), 1.0 per cent (11), 2.0 per cent (9), about 3.0 per cent (10), 1.52 per cent for males and 4.27 per cent for females (Wiedman and Campbell (14)), and 5.6 per cent for men and 10 per cent for women (Viswanathan (15)). Lesions at the base of the lower lobe are rare (9). There is a greater incidence in the adolescent and early age groups (5, 13, 14). Women are more frequently affected than men (10, 14, 15). The right side is more often involved than the left (13, 14). Except for Dunham and Norton (6), who were dealing primarily with Negroes, this type of disease has not been noted as more prevalent in one race or nationality than another. The lesions are usually exudative, bronchopneumonic, and finally caseous

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

in type (Fishberg (16)). They may thus simulate tuberculous bronchopneumonia or tuberculous pneumonia (6).

Various explanations for the occurrence of basal lesions have been offered. They have been classified as puerile in type (6), as a manifestation of blood-borne disease secondary to a lesion elsewhere in the body or lungs, as the result of massive infection through the respiratory tract (6), or as a result of rupture of a hilar or tracheobronchial lymph node into a large bronchus (8). The anatomical configuration of the chest and the physiological mechanism of respiration have been considered important (13, 15). Macklin (17) designates a superoretroradicular region in the chest, where there is minimum variation in respiratory volume, that is often the site of pulmonary disease. The fifth rib is regarded as the lower boundary of this region but it may be increased downward by costal type of respiration. The apex of the lower lobe lies within this region. The right lung is thought to be involved more often than the left because of the course of the right main bronchus and because of diminished excursion of the diaphragm on this side due to the liver (13).

Basal lesions sometimes absorb or undergo scar tissue formation (6) but more often there is cavity formation (6, 7, 13) and frequent spread of disease (13). This type of lesion is considered treacherous (7), and the prognosis grave (6, 8, 10). Collapse measures may alter the course of the disease (13, 8). For treatment, artificial pneumothorax is recommended (13, 8, 10), followed by phrenicotomy if the pneumothorax space is lost (8). Gordon and Charr (11) suggest that the combination of artificial pneumothorax and phrenic nerve surgery is unusually effective for this type of disease. Other authors (14) are disappointed in the results regardless of the type of collapse therapy employed.

MATERIAL

The impression gained was that the outlook for this type of case is unfavorable. It was thought that a study of those cases that had been under treatment sufficiently long ago to warrant conclusions might give some information as to the most effective method of treatment and also as to prognosis.

During the six and one-half years between October, 1929 and July, 1936, 3,597 new patients were admitted to the Sanatorium. Seven hundred and ninety-five of these were children.

For comparative purposes 664 of the children with first infection type of tuberculosis were tabulated according to the location of the lesion as given by the roentgenologist as: above the root, at the root, and below the root. This is shown in table 1.

The area above the right root was more often involved than other areas in the lungs. The right base was involved about three times as frequently as the left. This corresponds fairly with the incidence of right and left (76 per cent and 24 per cent, respectively) base involvement among adults, in the present series. Among the adults, the lower lobes were involved in 1.8 per cent of the cases, while among the children

TABLE 1

Location of disease in 664 children

	RIGHT		LEFT		BILATERAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Upper	139	20.9	83	12.3	39	5.8
Root	102	15.3	48	7.2	32	4.8
Base	95	14.3	33	4.9	6	0.9
Fluid	30	4.5	14	2.10	2	0.3
Upper and base	8	1.2	10	1.5	6	0.9
Other combinations			4	0.6		
Miliary			13	1.97		

the incidence was approximately 20 per cent. The distribution of basal involvement in relation to sex was not determined.

Of the 2,802 patients with adult or reinfection type tuberculosis, 52, or 1.8 per cent, were found to have lower lobe disease These cases form the basis of the present study. In the selection of cases, an attempt was made to take as clear-cut basal type lesions as possible, to eliminate controversy as well as to give a more accurate study. Cases presenting multiple pulmonary lesions were discarded unless some previous film demonstrated a preëxisting lesion in the lower lobe. Cases with disease in the lower half of the lung and near the anterior chest wall, as demonstrated by stereoscopic films, were likewise discarded. In several instances the location of the disease was evident after artificial pneumothorax had been established.[2] In none of the cases was there disease in

[2] In three instances stereoscopic films were not available. One case presented a 4 cm. cavity situated in the right midlung field at the level of the third rib anteriorly or the seventh

any other part of the homolateral lung. Fifteen cases showed a variable amount of disease in the contralateral lung, the majority minimal in extent. Three of these were considered as old lesions, possibly antedating the present basal lesion. They have not changed during the years of observation. The remainder were considered as secondary to the basal lesion since the majority of them cleared spontaneously after the original basal lesion was brought under control. In one case only was there definite evidence, at the time of admission, of existing or previous extrapulmonary disease. This patient had had a tuberculous kidney removed, in another institution, two years prior to admission with a lower lobe pulmonary lesion. He had also a small, fibrotic, nonchanging lesion in the apex of the contralateral lung.

Forty-nine of this series of patients were white and 3 were colored. Eighteen were male and 34 were female. Ages varied from ten to fifty-nine years, with 38 (73 per cent) of the group being between the ages of fifteen and thirty years. Twelve were classified as having minimal disease, 20 were moderately advanced, and 20 were far advanced. In 38 cases the disease was predominantly exudative, in 8 it was mixed in type, and in 6 it was predominantly productive. In 31 cases cavitation was present and varied from 1 cm. to 9.5 cm. in diameter. The average was about 3.5 cm. The right lung was originally involved in 40 of the cases, and the left in 12. The interval between onset of symptoms and diagnosis or hospitalization varied from two weeks to two, three and six years. If the 3 latter, as well as 3 asymptomatic contact cases are omitted, the average duration of symptoms was 5.5 months. Onset was acute in 31 cases and insidious in 21. Nothing of outstanding significance was noted in the laboratory data or symptoms that would distinguish this group of patients from those having similar disease in other areas of the lung. A positive sputum was obtained from 47 of the 52 cases, in 3 by culture only.

In the series, twenty different occupations were represented. It is probable that the distribution among the occupations reflects the age group to which the patient belonged. The various nationalities represented are indicative of the sanatorium population rather than showing a greater prevalence of this type of tuberculosis in any one of them. In 26 cases there was no known contact. In 5 cases a source outside the family was indicated, and in 21 cases at least one other member of the

interspace posteriorly. Two cases had minimal lesions on the right side at the level of the fourth rib anteriorly or the eighth rib posteriorly. In these three cases the lesion was probably in the right middle lobe in one and possibly so located in two.

family (most often a brother or the mother) had tuberculosis and at some time was a possible source of contact. In 2 cases, father and daughter aged fifty-nine and eighteen years respectively, the lesions were almost identical.

The type of disease exhibited by this group of patients ranged from small (minimal) fibrotic lesions to soft, exudative and rapidly progressing (almost fulminating) disease. The latter type is represented by 3 cases that were considered hopeless when they were admitted, but who were given such treatment as they could tolerate. All progressed steadily to death. The majority of the cases was bronchopneumonic, pneumonic or excavating in type.

TREATMENT AND RESULTS

Often it is difficult to evaluate accurately the effect of a given form of treatment, such as pneumothorax, when some other form of treatment, such as phrenic surgery, is added relatively soon after the first procedure is instituted. This is particularly true in this Sanatorium where collapse is regarded as a program and where one procedure may follow another promptly because our immediate objectives are closure of cavity and conversion of sputum. The principal procedures used, in addition to bed-rest, have been phrenic surgery (both crushing and evulsion), artificial pneumothorax and the combination of these two. In the present series, the patients were in the Sanatorium an average of 1.3 months before collapse measures were instituted. For those who received initial phrenic surgery, an average of six months elapsed before pneumothorax was begun. For those who received initial pneumothorax, an average of 4.5 months elapsed before phrenic surgery was added.

Table 2 gives the classification of the cases and the procedures used in the treatment of the side showing the initial or original lesion. For those cases that recovered satisfactorily the procedure used is designated as effective. Consideration of those cases receiving bed-rest alone for the initial lesion and those receiving bilateral surgical therapy will be found in the text.

Considering the 12 minimal cases as a whole, half of the cases that received phrenic nerve surgery alone recovered satisfactorily. In the minimal group, the cases receiving the combination of phrenic nerve surgery and artificial pneumothorax are the ones that did not improve with phrenic surgery alone. Three of the 4 patients that received the combined procedures recovered satisfactorily. No case in this group

received artificial pneumothorax alone. One patient died of progressive disease after leaving the Sanatorium.

Among the 20 cases with moderately advanced disease, 6 of the 11 that received phrenic surgery alone, and 3 of the 8 that received artificial pneumothorax alone recovered satisfactorily. Of the 9 cases that received combined phrenic surgery and artificial pneumothorax, 6 recovered. Two patients died in the Sanatorium.

Among the 20 cases having far advanced disease, 6 received phrenic surgery alone and none of them derived benefit from it. Of the 14 cases that received artificial pneumothorax alone, 3 recovered satisfactorily.

TABLE 2

Classification of patients with method of treatment

	NUMBER CASES	BED-REST ALONE*		PHRENIC CRUSH ALONE		PHRENIC-ECTOMY ALONE		ALL PHRENIC SURGERY		PNEUMO-THORAX ALONE		PHRENIC AND PNEUMO-THORAX		THOR-ACO-PLASTY*		DIED	STILL IN SANATORIUM
		Number	Effect	Number	Effect	Number	Effect	Number	Effect	Number	Effect	Number	Effect	Number	Effect		
Minimal	12	4	4	4	2	4	2	8	4			4	3				
Moderately advanced	20	1	1	3	2	8	4	11	6	8	3	9	6			2	
Far advanced	20			2	0	4	0	6	0	14	3	15	12	1	1	2	
Total	52	5	5	9	4	16	6	25	10	22	6	28	21	1	1	4	5
Per cent entire series			9.6		7.6		11.5		19.1		11.5		40.3		1.8	7.6	9.6

* See text.

Fifteen patients received combined phrenic surgery and pneumothorax and 12 of them recovered. The one thoracoplasty case is satisfactory.[3] Two patients in this group died of their disease in the Sanatorium.

For clarity, the cases are grouped according to the method of treatment employed. Five patients were left at bed-rest alone, 2 of these refused treatment, and 2 had small fibrotic lesions (that did not change during their residence in the Sanatorium) and were not offered surgical treatment. One patient had peritonitis in addition to the pulmonary lesion and both conditions cleared simultaneously. Insofar as the lesion on the original side is concerned, there was eventual clearing or scarring

[3] Subsequent to this evaluation, as of December, 1938, this patient's sputum has again become positive.

without further treatment. However, 2 cases later had spread of disease to the contralateral lung requiring active surgical therapy. One patient has had no exacerbation of disease during a period of six years, and 2 patients could not be traced.

Four patients of 9 who had phrenic crushing alone and 6 of 16 who had phrenicectomy alone recovered from their disease; that is, 10 of 25 cases that received phrenic surgery alone recovered. Twenty-two patients received artificial pneumothorax as the initial procedure and 6 recovered with this procedure alone. Twenty-eight patients received combined phrenic surgery and artificial pneumothorax and, of these, 21 recovered.

In relation to the entire series of 52 cases, the percentage of patients recovering under the various forms of treatment were: bedrest alone, 9.6; phrenic nerve crushing, 7.6; phrenicectomy alone, 11.5; (19.1 per cent for all phrenic nerve surgery); pneumothorax alone, 11.5; combined phrenic surgery and pneumothorax, 40.3; and thorocoplasty, 1.8. Patients still under treatment, 9.6 per cent and dead, 7.6 per cent.

BILATERAL DISEASE AND CONTRALATERAL THERAPY

Twenty-two patients in the series had evidence of spread of disease into the contralateral lung; 15 of these were present at the time of admission and 7 occurred in the Sanatorium. Spread occurred from three months to two years after the onset of symptoms, the majority occurring between three and six months. The percentage of spread from right lung to left was slightly greater than from left to right. The new lesion appeared most frequently in the contralateral apex. Spread occurred in 4 of the minimal cases, 5 of the moderately advanced and in 13 of the far advanced cases.

In 12 of the 22 cases with bilateral disease, the contralateral lesion cleared or fibrosed without surgical intervention. In none of them was there demonstrable cavity formation. Two patients were too ill for treatment and 8 received collapse therapy. Among the 8 cases treated with collapse, 3 were classified as having minimal disease at the time of admission, one was moderately advanced, and 4 were far advanced. Therapy administered for the original lesion was as follows: one patient had refused surgical treatment, 2 received phrenic surgery alone, one artificial pneumothorax alone and 4 received both pneumothorax and phrenic surgery. In all 8 cases artificial pneumothorax was given on the contralateral side. In one case the disease had not progressed to cavity formation, but pneumothorax was given because diaphragmatic paralysis

was impossible due to an anomalous phrenic nerve. At the present time, 2 of the 8 patients are dead, one is in the Sanatorium, 2 are continuing their cure at home, 2 are working and one is untraced. The latter case had negative sputum and was considered improved when he left the Sanatorium to continue his cure in another state.

Among this group of 22 cases showing bilateral disease, 4 are now dead, 8 are working or are able to, 4 are still under treatment, 3 have been discharged only recently and 3 have not been traced.

OTHER PROCEDURES

Among the patients receiving artificial pneumothorax, 11 developed an effusion, during treatment, sufficient to require aspiration. Two additional cases developed a small amount of fluid when pneumothorax was discontinued. The nature of the fluid in these 2 cases is not known. In 8 of the 11 cases where aspiration was required, tubercle bacilli were found in the fluid, either by culture or by direct smear.

Closed internal pneumonolysis was done on 3 cases in the entire series. Twice it was done to increase the degree of collapse and once as a prophylactic measure. In the latter case, disease had been controlled by combined phrenic surgery and pneumothorax, but the patient originally had a 6.5 cm. cavity.

Bronchoscopic examination has been made on 6 cases. In 3 tuberculous ulceration was present. One of these was first examined at another institution five years ago. At that time a small ulcer and a small tumor were found. The latter was removed. Recent examination in this case revealed a normal tracheobronchial tree. Two cases were examined because of recurring positive sputum. In both cases there was apparently adequate collapse of the lung and the pulmonary lesion appeared to be clearing. Both are still under treatment for their tracheobronchial disease. In 3 cases a normal tracheobronchial tree was found. One was examined as a routine measure preceding thoracoplasty and 2 because of occasional positive sputum. One of these later became negative and has been discharged from the Sanatorium. The other has bronchiectasis.

Contrary to the experience of Dunham and Norton (6), extrapulmonary disease has not been a common occurrence in this series. Postmortem examination was made on 2 cases. One of these, in addition to the localized pulmonary lesion and empyema, showed generalized peritoneal and intestinal involvement. In the other, disease was limited to

the lungs. In one far advanced case, the larynx, ears and intestine were successively involved. One patient had peritonitis, presumably tuberculous. Three additional cases had respectively, a history of "rectal abscess," mild cervical adenitis and enteritis, but in none of them was the condition proved to be tuberculous.

CLASSIFICATION OF PATIENTS ON ADMISSION AND DISCHARGE

Comparison of the classification, at the time of admission, of the patients having basal tuberculosis with the general adult Sanatorium admissions for the years 1930 to 1937, inclusive, is given in table 3.

Forty-seven patients of the series with basal lesions have been discharged from the Sanatorium. In 38 of them, sputum was negative by

TABLE 3

Classification of patients on admission

Admissions 1930–1937 (inclusive)

	GENERAL ADMISSIONS		BASAL LESIONS	
	Number	Per cent	Number	Per cent
Minimal	668	18.2	12	23
Moderately advanced	1,061	28.9	20	38.4
Far advanced	1,730	47.2	20	38.4
*	200	5.4		
Total	3,659	99.7	52	99.8

* Extrapulmonary tuberculosis, admitted for observation, bronchiectasis, silicotuberculosis, etc.

direct smear in 11 (cultures were not made), and negative by culture or guinea pig inoculation, or both, in 27. Classification at the time of discharge is compared with that of the general adult discharges during the years 1930 to 1937, inclusive, in table 4.

PRESENT STATUS OF PATIENTS

The discharged patients have been followed, or traced insofar as was possible, from one to six years since they left the Sanatorium. Their present status is given in table 5. Two additional patients have died, probably of tuberculosis. One has been readmitted and found to have tracheobronchial disease and has recently shown spread to the contralateral lung. At the present time, 6, or 11.5 per cent, of the series are dead, 6 are still in the Sanatorium, and 40, or 76.9 per cent, are at home.

It has been impossible to trace 8 of the 40 cases; 3 were known to have left the state.

Artificial pneumothorax has been discontinued in 9 cases. It had been carried from 3.5 to 5.5 years, an average of 4.3 years. Air has been

TABLE 4

Classification of patients on discharge

Discharges 1930–1937 (inclusive)

	GENERAL DISCHARGES		BASAL LESIONS	
	Number	Per cent	Number	Per cent
Apparently arrested	1,245	33.6	22	42.3
Quiescent	648	17.5	10	19.2
Improved	587	15.9	6	11.5
Unimproved	695	18.8	5	9.6
Died	349	9.4	4	7.6
*	178	4.8	5†	9.6
Total	3,702	100.0	52	99.8

* Stay too short to note change, pneumonia, lung abscess, etc.

† Still in the Sanatorium.

TABLE 5

Present status of the series of 52 cases

CLASSIFICATION OF DISEASE	ABLE TO WORK AT								UNDER TREATMENT		RECENT DISCHARGE	NEW LESION	DEAD	UNTRACED	TOTAL
	Housework	Secretary	Factory	Laboratory	Farm	School	Not stated	Total	Pulmonary Disease	Bronchial Disease					
Minimal	1*			1		2	4	8		1		1	1	1	12
Moderately advanced	3		1			3	2	9	1	1	2		3	4	20
Far advanced	3*	2	1		1	1		8	3		4		2	3	20
Total	7	2	2	1	1	6	6	25	4	2	6	1	6	8	52

* One patient in this group has borne one child.

discontinued for from one to four years and at the present time none of these patients have shown exacerbation of their disease.

SUMMARY AND CONCLUSIONS

The duration of symptoms before diagnosis or hospitalization, in this group of cases, varied from two weeks to several years. Although the average duration of symptoms was 5.5 months, 40 of the group were

moderately or far advanced, 31 had cavitation varying from one to 9.5 cm. in diameter, and 22 showed evidence of spread of disease to the contralateral lung. In a number of cases the time of spread could be estimated and, while it varied from three months to two years, the majority were between three and six months. In comparing the series of basal cases with an equal number of comparable cases[4] that had initial disease in the upper half of the lung, 22 of the former and 12 of the latter showed spread of disease to the same or to the contralateral lung. From this it appears that basal lesions tend to early and rather large cavity formation, and to earlier and more frequent spread than lesions in the upper half of the lung.

Two of the 5 cases left at bed-rest alone had small fibrotic lesions, and in 2 others there was spread of disease to the contralateral lung. Although the group is small, it does not seem safe or justified to trust basal lesions to bed-rest alone.

Among the minimal and moderately advanced cases, half of those receiving phrenic surgery alone recovered. It is of interest to note that, among the moderately advanced cases, 6 of the 11 that received phrenic surgery alone recovered, while 3 of 8 that received artificial pneumothorax alone recovered. This suggests that among minimal and moderately advanced cases crushing of the phrenic nerve might well be tried first for a short time before the induction of artificial pneumothorax.

None of the far advanced cases derived benefit from phrenic nerve surgery alone. Of the 22 cases receiving pneumothorax alone, 6 recovered, while of the 28 that received both pneumothorax and phrenic surgery, 21 recovered. This suggests that in far advanced cases artificial pneumothorax should be attempted first with a view to adding phrenic surgery relatively soon.

In the entire series of 52 cases, satisfactory results were obtained in 16, using one procedure alone; 10 of these received phrenic surgery alone and 6 received artificial pneumothorax alone. Satisfactory results were obtained in 21 cases using the combined procedures. This difference in favorable results warrants the use of both phrenic nerve surgery and artificial pneumothorax in combination wherever possible. It also bears out the suggestion of Gordon and Charr (11) that this combination of procedures is an unusually effective form of treatment for basal lesions.

[4] These were selected at random from the files and showed approximately the same type and extent of disease as the basal group. They were selected in the proportion of 12 minimal, 20 moderately advanced and 20 far advanced.

Because of the usual location of the lesion, thoracoplasty is not readily adaptable. Bronchoscopic examination should be made and pneumonolysis should be done when and where indicated.

In comparing the classification of patients having basal lesions with that of the general admissions it will be noted that the percentage in each group is quite similar. Classification at the time of discharge is also comparable when it is considered that a small group is being compared with a large one.

It appears that patients having lower lobe disease, when adequately treated, behave much the same as patients with disease elsewhere in the lung. It is possible that the impression that basal tuberculosis cases do not do well has led us to treat them quite strenuously and thereby obtain favorable results. If that is the case, it would seem wise to continue under that impression.

I wish to express my appreciation to Dr. H. S. Willis and Dr. B. H. Douglas for their suggestions and encouragement in this study and to Dr. C. C. Birkelo for his assistance in the selection of cases.

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THE UNEXPANDABLE LUNG[1]

I. Statement of the Problem[2]

JASON E. FARBER[3] AND N. STANLEY LINCOLN

By unexpandable or unexpanded lung is meant a lung collapsed by therapeutic pneumothorax which fails to reëxpand when attempts to do this are made, thus leaving a permanently collapsed lung with a so-called "dead pleural space." A broader interpretation would include those lungs that show no signs of reëxpansion between refills as seen on routine fluoroscopy and serial roentgenograms, and verified by intrapleural pressure readings. These lungs have usually been collapsed for several years. In most instances the pneumothorax has been complicated by an effusion. This study is not concerned with the large number of lungs collapsed by therapeutic pneumothorax that terminate successfully with complete reduction of the pleural space by means of displacement of the mediastinal structures and diaphragm, by retraction of the chest wall and by compensatory changes in the lungs. Our immediate concern in this study is limited to those permanently collapsed lungs with a permanent "dead pleural space." These patients are committed either to a lifetime of refills or to a surgical program aimed at obliteration of the "dead pleural space."

In our clinic 60 patients have had therapeutic pneumothorax induced and continued, and 73 patients whose pneumothorax was induced elsewhere have come to us for continuation of this type of therapy. In the first group there are 2 and in the second there are 12 patients with unexpanded lungs. If the experience of two other state tuberculosis hospitals (Homer Folks Tuberculosis Hospital and Hermann M. Biggs Memorial Hospital) is added we find that a total of 235 therapeutic pneumothoraces have been induced and of these, 11 patients now have unexpandable lungs. These figures in no way represent the true incidence of unexpanded lungs. They do show that in our experience

[1] From the Mount Morris State Tuberculosis Hospital, Mount Morris, New York.

[2] Presented at the annual meeting of the Eastern Division of the American Sanatorium Association, Mount Morris, New York, October 7, 1938.

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roughly 5 per cent of cases of therapeutic penumothorax result in unexpanded lungs, indicating that this is a significant clinical problem. Perhaps a better picture of the size of the problem is that in three state tuberculosis hospitals there has been inherited a total of 194 pneumothorax cases and of these 21 have unexpanded lungs. We are currently faced, therefore, with the solution of the problems presented by 32 cases of unexpanded lungs collected during the three years that these hospitals have been in operation.

Although the literature on therapeutic pneumothorax is voluminous, there is very little, especially in the American literature, which considers end results and late complications. In a study of 100 pneumothorax patients from one to eighteen years after expansion, Packard (1) noted that in the majority of cases there was not complete reëxpansion of the diseased lung but that compensatory changes in the chest obliterated the pleural cavity. Evidently in this series there were no cases of unexpanded lungs with residual "dead pleural spaces." Packard suggested the use of phrenicectomy preliminary to reëxpansion and the necessity of thoracoplasty to relieve symptoms incident to mediastinal displacement.

Dundee (2) has classified the lungs under consideration for reëxpansion, apparently based on (*a*) the extent and character of the original lesion, that is, the amount of pulmonary destruction, (*b*) the degree of fibrosis and pleural thickening, and (*c*) the mobility of the mediastinum. Dundee describes certain of these lungs as "collapsed and atelectatic, with frequent recurrences of hydropneumothorax with a fixed mediastinum." He also recommends, as useful, thoracoplasty with phrenic avulsion as the best method of terminating treatment in these cases. Eglee and Jones (3) reviewed 100 reëxpanded cases and stated that "eight cases have not wholly reëxpanded even though pneumothorax was discontinued two years ago." Nalbant (4) discusses the effect of pleural effusions complicating artificial pneumothorax and cites the subsequent difficulty in reëxpansion. Rubin (5) notes that in his experience a "dead pleural space" rarely results unless a bronchopleural fistula is present. De Weck (6) described a collapsed lung terminated as a permanent hydrothorax after forty-four months because of failure to reëxpand. Barnwell (7) cited two cases in which attempts at reëxpansion of a collapsed lung were unsuccessful due to obstructive atelectasis produced by ulcerative tuberculous tracheobronchitis.

Veran (8) reviewed and studied the end results of 234 patients with

therapeutic pneumothorax. Eight cases were considered unexpandable (irreducible) either voluntarily, the so-called *collapsus impératifs*, or because it was impossible to reëxpand the lungs, the so-called *collapsus perpétuels*. In the first group—the voluntarily permanently collapsed lungs—attempts at reëxpansion precipitated asthmatic crises which the pneumothorax had stopped and reëxpansion also produced a pleuritic reaction with formation of fluid. In the second group reëxpansion was found impossible due to pleuropulmonary sclerosis. In these cases there remained a large gaseous pocket after a period of three to ten years.

The careful studies of Lindblom (9) on collapse therapy in experimental animals, and later (10, 11) correlated with human clinical material, outline the basis for our understanding of the unexpandable lung. This work has recently been reviewed by Pinner (12). Lindblom showed that uncomplicated pneumothorax does not produce in the lung any changes which impair its functioning to a significant degree. In some cases, a diffuse dry tuberculous pleurisy occurs and gives rise to pleural and interstitial fibrosis with its consequent impairment of pulmonary function. In cases complicated by a pleural effusion the pleural and interstitial fibrosis is on the whole proportionate with the volume and duration of the effusion. The fibrosis consequent upon the pleuritis or effusion involves first the pleura, then by extension along the pulmonary septa reaches deep into the pulmonary tissue resulting in interstitial fibrosis. This fibrosis is more intense when the effusion is purulent than when it is serous. In those cases in which there have been extensive or lasting exudates and marked pleural fibrosis, reëxpansion is impossible, and there is obligatory permanent maintenance of a hydropneumothorax or pyopneumothorax because of the lung's inability to expand against a tough pleural scar (Pinner (12)). That part of the lung which has not been involved in the pathological process does not, after the termination of the treatment, become the seat of fibrosis or any other change which might interfere with the functioning of the lung. The interstitial fibrosis consequent to the lasting effusions produces a more or less decided impairment of the functional capacity of the collapsed lung.

Aetiology: There are several causes of an unexpandable lung. For descriptive purposes these have been divided into intrinsic and extrinsic factors. By intrinsic factors are meant those acting within the bronchi and lungs. By extrinsic factors are meant those outside the lung but within the pleural cavity. These are listed as follows:

I. Intrinsic Factors
   A. Bronchial occlusion
   B. Massive intrapulmonary fibrosis
      1. Due to healing of large areas of tuberculous disease with fibrosis (collapse plus infection)
      2. Secondary to pleurogenic fibrosis
      3. Due to nonspecific fibrosis and suppuration, frequently secondary to bronchial stenosis

II. Extrinsic Factors
   A. Pleural (visceral) thickening due to
      1. Hydro-(pneumo-) thorax of long standing
      2. Pyo-(pneumo-) thorax of long standing
      3. Oleo-(pneumo-) thorax, therapeutic, of long standing
      4. Haemo-(pneumo-) thorax, of long standing
   B. Pleural adhesions
      1. Adherence of visceral pleura to parietal pleura
   C. Bronchopleural fistula (permanent)

III. Combinations of Factors I and II.

Individual cases present practically always a varying multiplicity of these factors, and not one single obvious cause. In any instance it is possible to state what these several factors are, but it is usually not possible to evaluate precisely the relative importance of each. Probably this can be established only by experimental methods.

Diagnosis: The diagnosis of a permanently unexpandable lung is made when a lung collapsed by therapeutic pneumothorax or following a spontaneous pneumothorax fails to reëxpand when reëxpansion is attempted and the pleural space is not obliterated when refills are stopped. It is noted in these cases that small amounts of air cause a marked change in intrapleural pressures. On fluoroscopy the lung appears fixed and does not change appreciably in volume with the respiratory cycle. Roentgenograms in inspiration and expiration will verify the fluoroscopic findings, and in addition will usually demonstrate a markedly thickened pleura. If refills are not continued the intrapleural pressure becomes increasingly negative, fluid often appears, or, if present, increases in amount, the so-called "effusion ex vacuo;" the mediastinum, if not fixed, shifts toward the affected side, and the diaphragm may rise. In time, retraction of the chest wall may occur.

Of greater interest and importance is the early recognition of factors

which may lead to an unexpandable lung. The following are offered for consideration in this connection:

1: Awareness that a collapsed lung may not be reëxpandable
2: Diminishing expansibility of the lung as seen on repeated fluoroscopy
3: Thickening of the visceral pleura noted on serial roentgenograms
4: Persistent effusion (all types) of appreciable amount and duration
5: Bronchoscopic evidence of bronchial stenosis
6: Closer attention to manometric readings

The amount of air absorbed between refills is a reflection of the anatomical and physiological state of the pleura. Changes in the elasticity and the absorptivity of the pleura of a collapsed lung are manifested by a significantly increasing interval between required refills, by a decreasing amount of air necessary at each refill to maintain the intrapleural pressure at a desired level, or by increasing changes in the mean intrapleural pressures by given amounts of air. These are warning signs to be heeded.

SUMMARY

The unexpandable lung is an unfavorable end result of therapeutic pneumothorax. A review of the literature does not permit a reliable statistical estimation of the frequency of this condition. In a limited experience roughly 5 per cent of cases of therapeutic pneumothorax terminate in unexpandable lungs, indicating that this is a significant clinical problem. This condition may be caused by factors within the lungs and bronchi designated as intrinsic, and by factors outside the lung but within the pleural cavity, designated as extrinsic. The intrinsic factors are chiefly massive intrapulmonary fibrosis and bronchial occlusion. The extrinsic factors are pleural thickening and pleural adhesions. Diagnosis is made when a collapsed lung fails to reëxpand. Factors leading to the early recognition of an unexpandable lung have been outlined.

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THE UNEXPANDABLE LUNG[1]

II. Case Reports

JASON E. FARBER[2] AND N. STANLEY LINCOLN

The unexpandable lung, an end result and complication of therapeutic pneumothorax, has been briefly described (1). To illustrate the problem the following 7 patients with unexpandable lungs have been selected for a detailed presentation.

CASE REPORTS

1: 52, E. H. D., white female, age 43, was found in January, 1928 to have a moderately advanced tuberculosis of the left lung with a positive sputum. In July, 1928 therapeutic pneumothorax of the left lung was initiated, and complicated in January, 1929 by an effusion. Patient was first seen by us in April, 1936. For the previous four years she had been clinically well and working as a social service worker. The pneumothorax had been maintained, the effusion having persisted despite repeated aspirations. Physical examination reveals restricted motion of the left hemithorax on respiration and signs interpreted as hydropneumothorax. On the right there are compensatory breath sounds. Roentgenograms of the chest (figure 1) show a diminished width of the left hemithorax. The mediastinum is totally shifted to the left. The parietal and visceral pleurae are markedly thickened. The left lung appears to be about 90 per cent collapsed. A small amount of fluid lies in the costophrenic sulcus. Sputum, seldom present, is negative for tubercle bacilli on concentration and culture. Repeated attempts at reëxpansion have proved unsuccessful. The pneumothorax has been maintained to date by refills of 25 to 50 cc. at intervals of five to eight weeks. Typical intrapleural pressures are −2+8, 50 cc., +14+22. The fluid has been periodically aspirated and replaced by air; it is serous and translucent and from it, on one occasion, tubercle bacilli were grown on culture. A fluoroscopic examination in January, 1939 shows the left lung to be fixed and inexpansile. There is a fluid level at the eighth interspace posteriorly. The diaphragm is at the tenth rib posteriorly and moves approximately 2 cm.

[1] From the Mount Morris State Tuberculosis Hospital, Mount Morris, New York.
[2] Meyer Memorial Hospital, Buffalo, New York.

Comment: This case presents a hydropneumothorax of ten years' duration, now permanent and obligatory. The collapsed lung is immovable and fixed. This is due to extensive pleural fibrosis. Whether there is intrapulmonary fibrosis cannot be determined. That such fibrosis, pleurogenic in origin, exists, is highly likely. Since the pulmonary parenchyma has not been visualized roentgenographically for ten years, the possible additional rôle of posttuberculous parenchymal fibrosis cannot be evaluated. It is important to note that insufflations of air are but infrequently necessary and that only small amounts of air cause marked changes in intrapleural pressure indicating an unyielding, stiff-walled pleural cavity.

2: 117, M. T., white female, age 39, school teacher, was diagnosed in September, 1932 as having advanced tuberculosis of the left lung with a positive sputum. Therapeutic pneumothorax on the left was started in February, 1933. In December, 1933 an effusion appeared in the left chest and since then has been present, in spite of frequent aspirations. In July, 1932 the patient had noticed wheezing on breathing, but this was apparently stopped by the pneumothorax until July, 1935. At this time a phrenicectomy was performed on the left and following this the wheezing again appeared. In April, 1936 patient came to the Mount Morris Tuberculosis Hospital. Physical examination revealed a woman who appeared in good health. Physical signs in the chest were: on the right, compensatory breath sounds, no râles; on the left, dulness throughout to flatness at the base, breath sounds were obscured by asthmatoid wheezes. A succussion splash was elicited. Her sputum was found to be positive. Roentgenograms of the chest (figure 2) show the upper part of the mediastinum and trachea slightly deviated to the left. The left lung is collapsed almost completely. Both visceral and parietal pleurae are markedly thickened. Fluoroscopic examination shows the lung to be fixed and inexpansile. The diaphragm is elevated and fixed. Fluid is present in the costophrenic sulcus. The pneumothorax was considered unsuccessful and it was decided to abandon it and perform thoracoplasty. Thoracoplasty was deferred because attempts at reëxpansion of the collapsed lung failed. No refills were given for five months during which time there was no evidence of reëxpansion. Instead there was a marked increase of the fluid in the pleural space. The pneumothorax has been maintained with refills of approximately 50 cc. at intervals of approximately four to five weeks. Intrapleural pressures vary typically as follows: −6−2, 50 cc., +8+16. Because of the persistent wheezing a bronchial lesion was suspected and bronchoscopy was performed. On the first bronchoscopy, December 5, 1936, the impression was stenosis and tuberculoma of the left main bronchus. On January 15, 1937 bronchos-

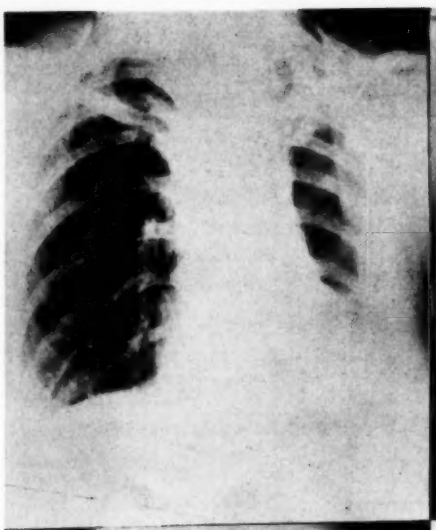

FIG. 1

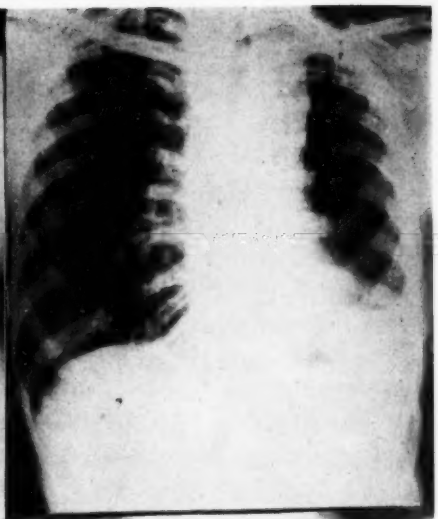

FIG. 2

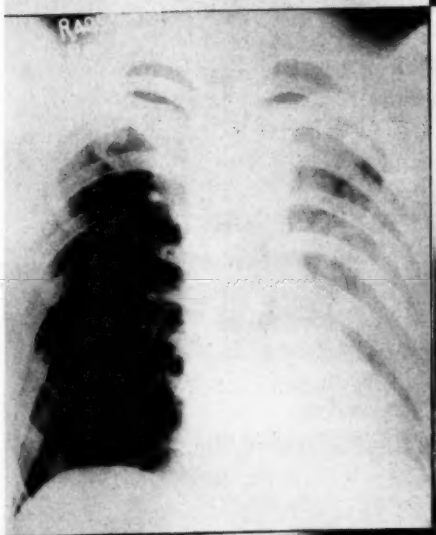

FIG. 3

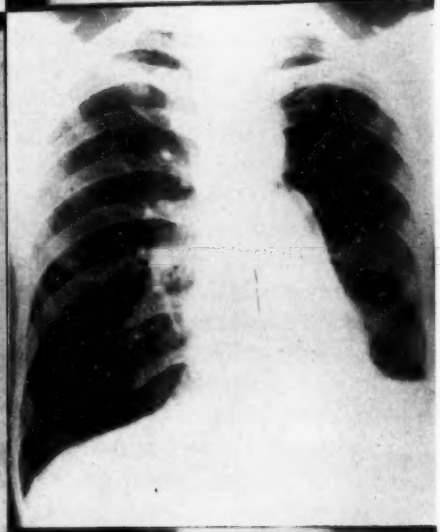

FIG. 4

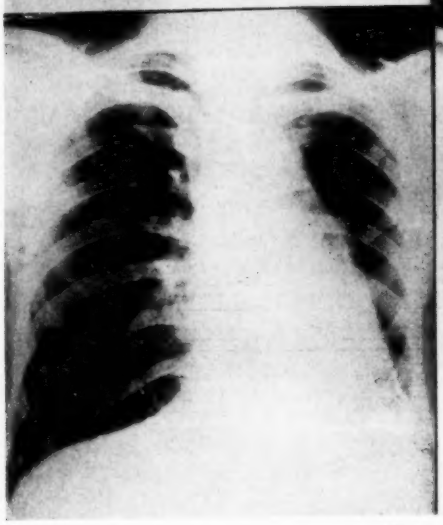

FIG. 5

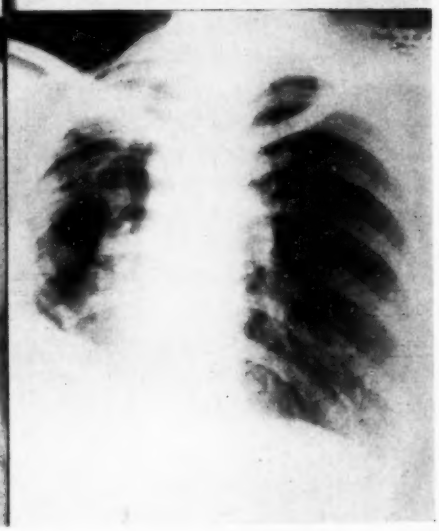

FIG. 6

FIGS. 1–6

copy revealed the orifice of the left main bronchus completely occluded by granulation tissue which on biopsy was found to be nonspecific.

Comment: The collapsed lung cannot be reëxpanded. The observable aetiological factors are: (*1*) thickening of the pleura probably consequent to an effusion of five and a half years' standing; (*2*) tuberculous bronchitis of seven years' duration with eventual bronchial occlusion. The precise contribution of each of these factors to the final immobility of the lung cannot be evaluated. Again parenchymal fibrosis, which cannot be directly observed, can only be postulated.

3: 2757, J. E. F., white male, age 28, physician, was found to have a moderately advanced tuberculous lesion of the left lung in August, 1934. The onset, haemoptoic in character, was rapidly followed by extensive pneumonic infiltration throughout the left lung (figure 3). Therapeutic pneumothorax was initiated in August, 1934 and complicated by a copious pleural effusion in December, 1934. The fluid was allowed to remain in the pleural space for approximately eight months during which time it slowly disappeared. On five occasions since then effusions have reappeared in appreciable amounts, each time persisting on an average of four months. Since 1937 the fluid has been periodically aspirated in order to keep the pleural space as dry as possible. Reëxpansion was attempted in January and February, 1936 but was unsuccessful. Refills had been discontinued for seven weeks. Instead of reëxpansion of the lung occurring both mediastinum and collapsed lung shifted to the left. This resulted in a brief illness with fever, malaise, pain in the chest and the appearance of more fluid. Since then the pneumothorax has been maintained with refills at intervals of three to four weeks. There has been progressive diminution in the amount of air needed at successive refills, until finally 50 to 75 cc. of air results in a change in intrapleural pressure from −10−6

FIG. 1. Case 1. An unexpandable lung on the left, collapsed about 90 per cent; the mediastinum is displaced to the left, fluid is present in the costophrenic sinus. Note the dense shadow of the collapsed lung due to pachypleuritis.

FIG. 2. Case 2. An unexpandable lung on the left with thickened visceral pleura. The mediastinum and trachea are deviated to the left, fluid is present in the costophrenic sinus.

FIG. 3. Case 3. Massive collapse of the left lung following several large haemoptyses. The mediastinum is displaced to the left, the diaphragm is elevated.

FIG. 4. Case 3. The same patient sixteen months later, during which time hydrothorax has twice occurred. Note the marked density of the collapsed lung. The mediastinum is displaced to the left.

FIG. 5. Case 3. The same patient three years later. There is displacement of the mediastinum to the left and the diaphragm is elevated.

FIG. 6. Case 4. An unexpandable lung, Bucky diaphragm technique with an opaque plastic on the left side. Note the deviation of the trachea and the bronchi, also the elevated diaphragm. The mediastinum is displaced to the right.

to +1+5. The patient has been working since January, 1936. He is asymptomatic and has been afebrile except at the time of the onset of the effusions. The patient notices a few days before a refill a sensation of pulling inside the chest, slight dyspnoea on exertion, and often epigastric distress. These symptoms disappear following a refill. On physical examination in February, 1937 the patient appears in good health. There is obvious reduction in the size of the affected hemithorax. There are the usual signs of hydropneumothorax. On fluoroscopic examination there is seen only a very slight degree of movement of the collapsed lung. The lung is adherent posteriorly along the vertebral gutter. The diaphragm is elevated and fixed. Serial roentgenograms of the chest (figures 4 and 5) reveal progressive displacement of the mediastinum to the left and progressive elevation of the diaphragm on that side. Sputum, scant in amount, has been persistently negative on both concentration and culture since the induction of the pneumothorax. The pleural fluid of March, 1937 was serous in character, and from it only tubercle bacilli were cultured.

Comment: This case is analogous to case one. In this instance, however, the immobility of the lung was recognized eighteen months after the induction of the pneumothorax and fourteen months after the appearance of the effusion. It is known that there was extensive pulmonary disease but whether this was followed by extensive parenchymal fibrosis is hypothetical.

4: 428, A. L. M., white female, age 32, a nurse, was found in March, 1930 to have an advanced tuberculous lesion of the right lung with cavitation in the upper third, with a positive sputum. During December, 1930 and January, 1931 the patient had several haemoptyses. Therapeutic pneumothorax of the right lung was initiated in January, 1931. The patient resumed nursing work in January, 1933. At this time she was asymptomatic and afebrile and the sputum was negative on concentration. In December, 1936 her physician abandoned the pneumothorax. Physical signs in the chest at that time were those of pneumothorax on the right. No signs suggesting bronchial stenosis or occlusion were elicited. Breath sounds can be heard anteriorly. On questioning, the patient denies any wheezing or asthmatoid symptoms. On fluoroscopic examination the right leaf of the diaphragm appeared high at the lateral chest wall and moved barely one-half cm. Roentgenograms of the chest (figure 6) showed the right hemithorax to be decreased in size and there was narrowing of the interspaces especially posteriorly. The mediastinum was displaced to the right. On the right a pneumothorax pocket was seen. On a standard flat film the pleura appeared markedly thickened below the level of the third rib and no lung detail was visualized. No fluid level

was seen. Several months after abandoning the pneumothorax the patient began to experience pain in the right chest, a sensation of pulling, dyspnoea on slight exertion, palpitation and tachycardia. Fluoroscopic examinations revealed that further reëxpansion was not occurring, and fluid was appearing in the pleural space for the first time. The patient then elected to have plombage rather than to continue refills. This was carried out. Since then the patient has felt reasonably well and is asymptomatic except for some dyspnoea on exertion.

Comment: In this case a lung was found to be unexpandable five years after the induction of pneumothorax. There is no evidence of a bronchial lesion and there is certainly no bronchial obstruction. There had been no effusion (this only appeared subsequently on attempts at reëxpansion). There is, however, a thickened pleura which obscures parenchymal detail. The aetiology of this unexpandable lung is therefore very probably pleuritis sicca and intrapulmonary fibrosis attendant upon the healing of rather extensive disease of the lung.

5: 1235, M. S., white female, age 30, housewife, was found in April, 1931 to have pulmonary tuberculosis. During the following five years patient was hospitalized intermittently at various sanatoria and was admitted to this hospital September 12, 1936 with a diagnosis of advanced fibro-ulcerative tuberculosis of the right lung, with positive sputum. On October 17, 1936 therapeutic pneumothorax of the right lung was initiated. By means of positive pressures the lung was collapsed roughly 80 per cent; the sputum, however, remained positive. On May 27, 1937 a copious pleural effusion appeared collapsing the lung almost completely. Aspiration revealed a translucent, serous fluid. The effusion persisted until November, 1937, reappeared April 19, 1938 and has been present since in spite of repeated aspirations. The fluid did not change in character. On April 18, 1938 it was decided to reëxpand the lung and do a thoracoplasty, since the pneumothorax of eighteen months' duration was ineffective in converting the sputum. However, attempts at reëxpansion during the ensuing six months were unsuccessful. The fluid was repeatedly aspirated, leaving low intrapleural pressures. The fluid constantly and rapidly reappeared. Physical signs in the chest at that time included bronchial breathing in the right apex, elsewhere throughout breath sounds were absent. Roentgenograms of the chest on March 26, 1938 (figure 7) showed the right lung collapsed almost completely, and a fluid level just over the dome of the diaphragm. Both the visceral and parietal pleurae were thickened. Because of failure of reëxpansion of the lung, bronchoscopy was performed September 1, 1938. This revealed that the opening of the right main bronchus was stenosed, and the remaining

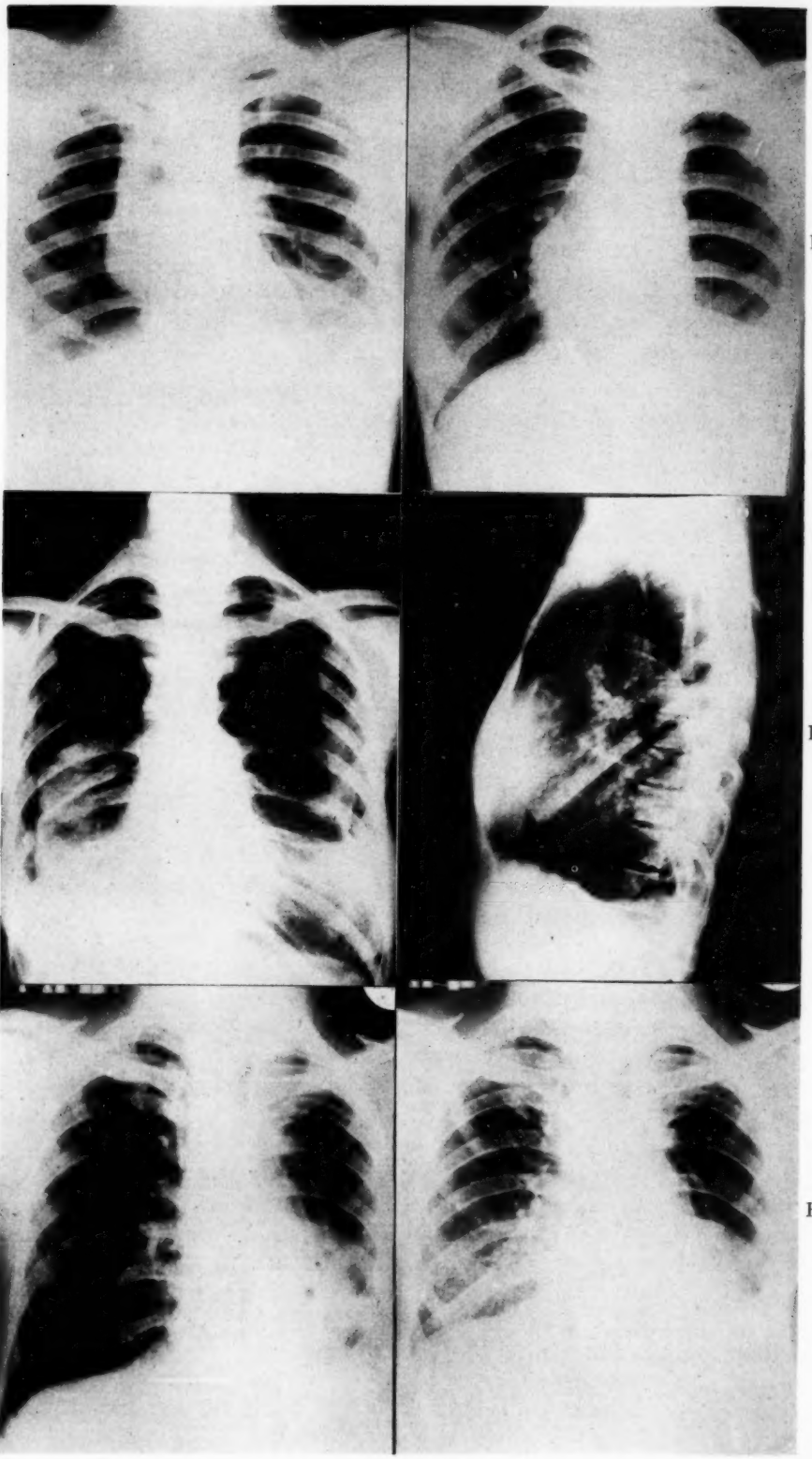

FIG. 7

FIG. 8

FIG. 9

FIG. 10

FIG. 11

FIG. 12

FIGS. 7–12

lumen was filled with tenacious, grayish, purulent secretions, and the mucosa was inflamed. The bronchoscopist doubted that there was any respiratory exchange through the bronchus.

Comment: In this instance a lung is shown to be unexpandable after eighteen months of pneumothorax, during the last eleven months of which there was an abundant effusion. The established pathogenetic factors are: (*1*) thickened pleura, probably the result of an effusion; (*2*) bronchial stenosis. A postulated pathogenetic factor is parenchymal fibrosis. This seems likely since the primary pulmonary disease was thought to be fibroid in character. As mentioned previously there is also the possibility of pleurogenic intrapulmonary fibrosis.

6: 2205, H. L., white female, age 24, student, was diagnosed in 1930 as having advanced pulmonary tuberculosis with cavitation with positive sputum. In December, 1930 therapeutic pneumothorax of the left lung was started and in March, 1931 closed pneumonolysis was performed. In February, 1936 clear fluid was aspirated from the left pleural space; in June, 1936 the fluid was found to be milky and the presence of a bronchopleural fistula was demonstrated by the injection of gentian violet. The sputum was purple stained for two days but has not subsequently shown the dye. On admission, December 22, 1936, the patient appeared poorly developed and emaciated and was febrile. Examination of the thorax revealed signs of hydropneumothorax on the left. Breath sounds were everywhere absent on this side. Stereoscopic films of the chest showed the trachea displaced to the left, the heart rotated to the right. On the left the entire lung field and left cardiac shadow were obscured by a dense homogeneous shadow interpreted as thickened pleura, covering the entire left hemithorax. Aspiration of the left chest revealed a thick, opaque, purplish colored fluid that showed relatively few cells on smear; culture for secondary organisms was negative but acid-fast bacilli were seen on smear. Concurrently the sputum was negative for tubercle bacilli and

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FIG. 7. Case 5. An unexpandable lung, totally collapsed. The pleura is markedly thickened. An effusion is present.

FIG. 8. Case 6. An unexpandable lung, totally collapsed. The mediastinum is displaced to the right. Pachypleuritis is present.

FIG. 9. Case 7. Bilateral unexpandable lungs and bilateral hydropneumothorax. Note the fluid levels.

FIG. 10. Case 7. Lateral view of the chest of the same patient one year later, Bucky-Potter diaphragm technique.

FIG. 11. Case 3. A flat film of the chest on deep inspiration. Note that there is only a slight degree of expansion of the collapsed lung.

FIG. 12. Case 3. A flat film of the chest on forced expiration taken the same day. Note the shift of the heart and mediastinum to the right.

contained no dye. The fluid was repeatedly aspirated, always returning, but gradually thinning out and becoming more serous. Clinically the patient improved remarkably. Serial roentgenograms (figure 8) showed the persistent pyopneumothorax and the markedly thickened visceral and parietal pleurae. For a period of eight months repeated attempts to reëxpand the lung met with failure. Intrapleural pressures have been maintained highly negative (−24−26). Fluoroscopic examinations show the left lung to be fixed and immobile and inexpansile on respiration. The left leaf of the diaphragm is fixed. The patient was not bronchoscoped.

Comment: In this case there is an unexpandable lung after six years of pneumothorax and an effusion of at least eleven months' duration. The definite aetiological factors preventing reëxpansion are a thickened fibrotic pleura due to a long standing effusion and a bronchopleural fistula. The latter probably contributed to the end result in the following ways: (*1*) It converted a serous effusion into a purulent one, and purulent effusions produce more pleural fibrosis than serous effusions. (*2*) It probably caused more complete collapse of the lung making obliteration of the pleural space more difficult. (*3*) It undoubtedly led to massive dissemination of infectious material throughout the collapsed lung with resulting irreversible changes.

7: 1311, L. D., white female, age 26, office clerk, was admitted on August 18, 1936 complaining of shortness of breath and wheezing since 1929, and a history of pulmonary tuberculosis dating back to September, 1932. The patient had been hospitalized elsewhere from January, 1933 to August, 1936. Therapeutic pneumothorax was initiated on the left side on April 25, 1935 because of a moderately advanced parenchymatous lesion and a positive sputum. In August, 1935 the pneumothorax was complicated by an effusion which, except for a very brief interval, has since been present. In February, 1936 an annular shadow was noted in the right lower pulmonary field and therapeutic pneumothorax was initiated. The following day an effusion appeared on the right and since then has been present. On admission the patient appeared poorly developed, undernourished and chronically ill, with cyanotic lips and finger nails. Sputum was positive. Physical signs were those of bilateral hydropneumothorax. In addition, sibilant and sonorous râles heard over the right base and rhonchi palpable over the left chest suggested bronchial lesions. Roentgenograms of the chest on admission (figure 9) show the mediastinum to be central in position. The right lung is collapsed approximately 60 per cent and is separated from the chest wall in its entirety, the apex of the lung being at the level of the second rib anteriorly. The visceral pleura appears thickened. A fluid level is the height of the tenth rib posteriorly. The outline of the

diaphragm is obscured because of the fluid. The left lung is collapsed approximately 60 per cent. The apex of the lung is at the level of the second rib anteriorly. The visceral pleura appears thickened below the level of the fifth rib anteriorly. The patient's clinical course has been stormy. She has frequently experienced paroxysms of extreme dyspnoea, wheezing and cyanosis. These paroxysms usually terminated with the expulsion of a mass of thick, frothy, sticky, tenacious sputum, followed by dramatic relief. It was felt that the patient's clinical picture suggested bronchial stenosis and bronchoscopy was considered. However, because of the patient's poor physical condition and the marked dyspnoea at rest, bronchoscopy was deferred. Vital capacity at this time was 700 cc. (20 per cent). Intrapleural pressures were as follows: on the right −24−10, on the left−18−6. Shortly after admission reëxpansion of both lungs was attempted without success. Deflations have been made at fairly frequent intervals since then and the fluid repeatedly aspirated from both pleural cavities. Intrapleural pressures have been maintained at approximately −26−6 on the right, and −22−6 on the left, but there has been no evidence of any appreciable degree of reëxpansion of either lung. The pleural fluid has been serous in character; no tubercle bacilli were demonstrated nor secondary organisms grown. On fluoroscopic examination motion of the lungs on inspiration and expiration can barely be discerned. The mediastinum and diaphragm are fixed. The lungs are adherent posteriorly and at the diaphragm (figure 10). Of considerable interest in this case are the blood counts. The haemoglobin on admission was 13 grams, red cell count was 4,070,000. There has been a progressive increase in both values until on May 23, 1938 the haemoglobin was 18.5 grams and the red cell count 6,230,000. The vital capacity has remained unchanged.

Comment: This case of unexpandable lungs is of unusual interest because the condition is bilateral. The condition was established on the right after nineteen months of pneumothorax and one year of hydropneumothorax, and on the left after seven months of hydropneumothorax. The visceral pleurae are thickened, again undoubtedly due to the effusions. There are very likely bronchial lesions, perhaps of seven years' duration.

DISCUSSION AND SUMMARY

It can be seen from the foregoing that the evaluation of pathogenetic factors leading to unexpandable lungs is difficult. In the first place, we are restricted to clinical observations entirely, no deaths having occurred in this series. Second, in regard to the important question as to the

changes occurring within the involved lung, roentgenology fails to be helpful because of the obscuring of the pulmonary fields by the thickened pleura. The best approach would seem to be to ascertain in each case which of the possible aetiological factors can be demonstrated to be present, and which are assumed to be present.

Thickening of the visceral pleura has been a constant factor in all cases. The cause of this pachypleuritis was serous effusions in five instances, an empyema in one instance, and in the remaining case, a pleuritis sicca. If these effusions or empyemata result from a bronchopleural fistula, then such fistulae, even if they subsequently close, must be looked upon as an important aetiological factor. (Case 6.) If the bronchopleural fistula remains patent, obviously the lung cannot reexpand. Adhesions between the visceral and parietal pleura may interfere with subsequent reëxpansion. Cases 1, 2 and 3 show adherence of the lung posteriorly to the chest paravertebrally and inferiorly to the diaphragm.

Undoubtedly massive intrapulmonary fibrosis prevents complete reexpansion of the collapsed lung. Even though difficult to demonstrate clinically, as stated above, experimental work and autoptic observations have shown that such occurs in cases of this type. As Lindblom pointed out, massive intrapulmonary fibrosis may be pleurogenic in origin, that is, by direct extension along the pulmonary septa from the pleural surface. That the healing of tuberculous foci may result in massive fibrosis is well recognized. Especially does this seem to be true in the combination of collapse plus infection (Pinner (2)). All these factors are present in these cases—extensive pulmonary disease, pleuritis and collapse. It is therefore highly probable that extensive intrapulmonary fibrosis exists in all the cases described.

Bronchial lesions may be a factor in the production of unexpandable lungs. If an occlusion is present, the sequence is obvious, atelectasis followed by irreparable and irreversible pathological changes making expansion impossible. Marked ulcerative tuberculous tracheobronchitis with bronchial stenosis may lead also to comparable changes. Barnwell (3) cited two cases in which "X-rays showed a progressive shrinkage of the collapsed and atelectatic lung" and autopsy confirmed this and the presence of the bronchial lesion. Nonocclusive stenotic tuberculous bronchial lesions may contribute by causing a nonspecific pneumonitis followed by extensive intrapulmonary fibrosis. Three cases of the pres-

ent series had bronchial lesions, two of which were bronchoscopically demonstrated.

There may be no symptoms associated with an unexpandable lung (case 1), or symptoms chiefly referable to respiratory or cardiac embarrassment may be present (case 4). These symptoms correspond to the well recognized symptoms that occur during and following the reëxpansion of lungs collapsed by therapeutic pneumothorax.

The physical signs accompanying an unexpandable lung are essentially those of pneumothorax, of fibrothorax and of hydropneumothorax. The signs are further modified if a bronchial stenosis is present.

Fluoroscopic examination, supplemented by inspiratory and expiratory roentgenograms (figures 11 and 12) of the chest, is very informative and most important. On fluoroscopy it can be seen that the lung does not expand on inspiration (cases 1 and 2), often rather there is a medial to lateral motion of the mediastinum and collapsed lung synchronous with the respiratory phases (cases 3 and 4). The collapsed lung appears dense and homogeneous, especially when a thickened pleura is present (cases 1, 2 and 5). The diaphragm on the affected side is usually elevated and moves slightly or not at all (cases 1 to 7).

The writers wish to express appreciation to Doctors Max Pinner and Aaron E. Margulis for advice and friendly criticism.

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CLOSED INTRAPLEURAL PNEUMONOLYSIS[1]

H. A. JONES

It is axiomatic that, when a pneumothorax fails to fulfill its purpose, additional measures should be taken to improve it or it should be abandoned. Moreover it will be shown that the majority of pneumothoraces which become effectual do so within three months of their induction. Therefore, if a cavity remains uncollapsed after three months of pneumothorax treatment, additional measures should be promptly considered.

Though ineffectiveness is of primary importance there are other objections, mainly born of it, to continuing a pneumothorax which falls short of fulfilling its purpose. The use of high pressures, for any reason, is generally considered to be hazardous and more liable to failure than success. Matson (1) states that, in his experience, spontaneous pneumothorax was 4 per cent more common in pneumothoraces with adhesions where high pressures were used. The incidence of tuberculous empyema is also definitely higher in such cases.

INDICATIONS FOR SEVERING ADHESIONS

What additional measures, other than increased pressures, may be used to improve the ineffectual pneumothorax? Practically and in short, these are two in number, namely, phrenic nerve crushing and closed intrapleural pneumonolysis. To these may be added intrapleural pneumonolysis by the open method, but it is generally conceded that this hazardous procedure is rarely advisable. In cases where there is extensive destruction of lung tissue it may be preferable to abandon the pneumothorax in favor of thoracoplasty. But, generally speaking, where operable adhesions are the cause of an ineffectual pneumothorax, closed intrapleural pneumonolysis is the supplementary procedure of choice.

Opinions vary regarding the respective merits of pneumonolysis and phrenic crushing as supplementary measures to an ineffectual pneumothorax. The latter operation has undeniable merit, is simple to perform, and its effect on the patient is rarely unfavorable. The effect on the

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inadequately collapsed lung is nevertheless uncertain and in this respect pneumonolysis is a superior measure. Severing of adhesions is followed by a relatively quick and sure result, and usually a more selective type of collapse is obtained than is possible with pneumothorax plus hemidiaphragmatic paralysis. The time factor is important both from a physical and economic standpoint. It is for these reasons that disagreement is expressed with the plan of routinely doing phrenic nerve operations and subsequently severing adhesions if the collapse is still unsatisfactory. Such a procedure is advisable only when thoracoscopic examination demonstrates that adhesions are operable at considerable risk. In such a case the phrenic nerve should be crushed first and the question of pneumonolysis would hang on the result so obtained.

As well as being an invaluable aid where there is ineffectual collapse, pneumonolysis is a justifiable procedure where an effectual pneumothorax has been established, but at the expense of a considerable volume of healthy lung. This applies particularly to patients with bilateral collapse who have dyspnoea. Pneumonolysis is indicated when a pneumothorax is effectual by a narrow margin and adhesions are exerting a pull on the diseased area; and likewise where a pneumothorax is becoming smaller on account of contraction of adhesions. The operation is occasionally indicated where a lung reëxpands rapidly between refills of air, thus threatening the maintenance of the pneumothorax. Downward pressure on the liver and stomach by the pneumothorax at times gives rise to severe symptoms. A more selective collapse may be obtained in such cases by division of adhesions and relief of symptoms brought about in this way.

DURATION OF PNEUMOTHORAX BEFORE SEVERING ADHESIONS

The length of time that an ineffective pneumothorax should be maintained before adhesions are severed is a variable period but most writers appear to favor an interval of from three to six months. I am firmly convinced that in many cases adhesions should be severed within one month of the induction of the pneumothorax. In my experience complications have been no more frequent when this has been done and the advantages of such an early effectual collapse are obvious. Where a pneumothorax is to be induced contralaterally it is desirable to obtain as effective and selective collapse as possible with a minimum of delay. Again, if X-ray films reveal numerous adhesions firmly holding out the diseased lung area after a month of pneumothorax treatment, it is not

likely that an additional three or four months of such treatment will bring about much improvement. Rather than resort to high pressures it is preferable to proceed with pneumonolysis at once. It is well known that some adhesions do stretch after six months of treatment, but the dangers of continuing with an ineffectual collapse (with or without high pressures) even this length of time are greater than possible complications of pneumonolysis.

With regard to complications of closed intrapleural pneumonolysis the main danger lies in injury to the lung causing bronchopleural fistula, spontaneous pneumothorax and tuberculous empyema. The commonest complication, but one which rarely causes trouble, is simple pleural effusion. Severe bleeding is rarely encountered. Disregarding the skill or experience of the operator, complications will usually vary directly with the difficulty of the operation, which again will depend upon the type of adhesions to be severed. Pneumonolysis is a simple operation where adhesions are thin and long but often difficult where they are thick and short. Indeed, some adhesions are too short for dividing with safety and in such cases the usual technique is not employed. The same situation prevails where a reflection of lung is attached to the chest wall. In both cases the attachment may be enucleated from the chest wall in a manner to be described later.

ANALYSIS OF 400 PNEUMOTHORACES BEFORE AVAILABILITY OF PNEUMONOLYSIS

Pleural adhesions prevent an adequate collapse in about 50 per cent of pneumothoraces, so that their division is a problem of primary importance. We have recently reviewed 400 successive pneumothorax patients who were treated prior to the availability of pneumonolysis and have ascertained that only 55 per cent became effectual, and that a successful end result was obtained in less than 50 per cent. Pleural adhesions were responsible for the majority of failures and it is estimated that more than 50 per cent of these could have been rendered effectual by pneumonolysis. The incidence of effusion and tuberculous empyema was notably greater in the ineffectual group. Eighty per cent of the clinically successful pneumothoraces required three months or less to become effectual. Of 60 patients who had received bilateral pneumothorax treatment 23 are considered arrested and 29 are dead. In the latter group operable adhesions appeared present on one or both sides in at least 15. Of the 23 arrested cases only 10 out of 46 pneumothoraces took longer than

three months to be effectual. Sixty-six successive thoracoplasty patients had had pneumothorax attempted but in only 24 was it established and in these the collapse was inadequate and thoracoplasty followed in from six months to two years. It is estimated that 40 per cent of this group would have avoided thoracoplasty if pneumonolysis had been available.

OPERABILITY OF ADHESIONS

Operability of adhesions can be determined only by thoracoscopic examination. By means of stereoscopic and oblique roentgenograms much useful information is obtained, but usually only an approximate idea of the nature of the adhesions is to be expected. Nevertheless, adhesions that appear operable by radiographic study are in the majority of cases so proved at thoracoscopy. Commonly, more adhesions are found by direct examination than are expected from films. The plan of procedure is accordingly dependent on the information obtained at thoracoscopy. If adhesions are found to be inoperable an opinion is made as to the advisability of continuing with the pneumothorax with increased pressures and possibly with a supplementary phrenic crush if this has not already been done. If the adhesions are suitable for division they are severed with the galvanocautery or high frequency current as preferred. The nature of the adhesion together with its relationship to lung, mediastinal structures, vessels and nerves determines its operability. As a general rule the operative risk varies directly with the length, thickness and construction of the adhesion. A long adhesion even though broad and thick is usually operable with safety wherever its parietal attachment. Severing of a short, thick adhesion, particularly when it is in close relationship to such a structure as the subclavian vein, is more hazardous. Cone shaped adhesions are presumed to contain lung tissue or possibly an extension of a cavity. By transillumination it is possible to visualize reflection of lung tissue but only if the adhesion is relatively thin. For adhesions that by their shape are presumed to contain lung tissue extending to the parietal pleura, or where such reflections are visible, the cold cautery technique as described by Coryllos and Ornstein is used (2). When a tongue of lung is attached to the chest wall with no demonstrable intervening adhesion this plan is also followed. It is interesting to note that as early as 1922 Jacobaeus (3), in referring to a large apical band, reported that "at first I tried only to loosen the pleura around the adhesion, partly bluntly with a chisel." Usually the parietal pleura is slightly bulged at the point where the adhesion or the

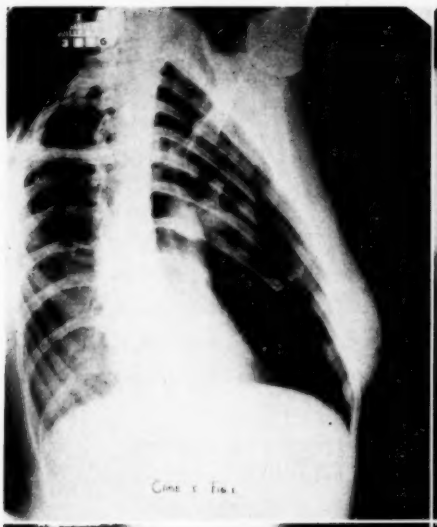

FIG. 1

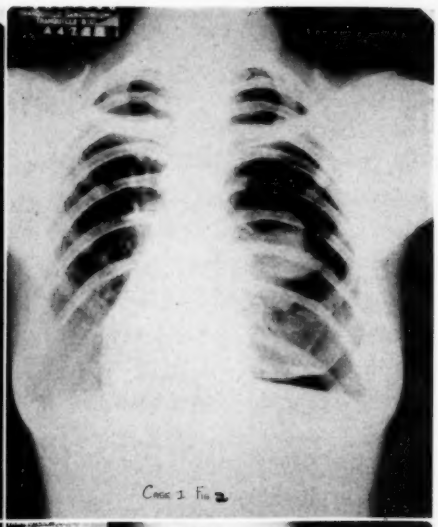

FIG. 2

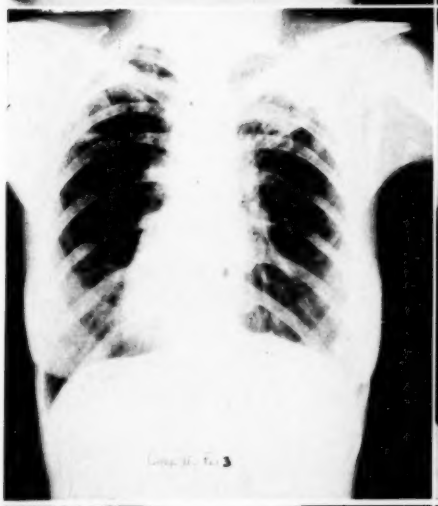

FIG. 3

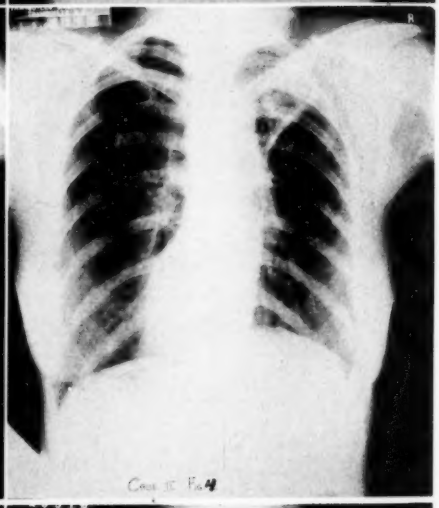

FIG. 4

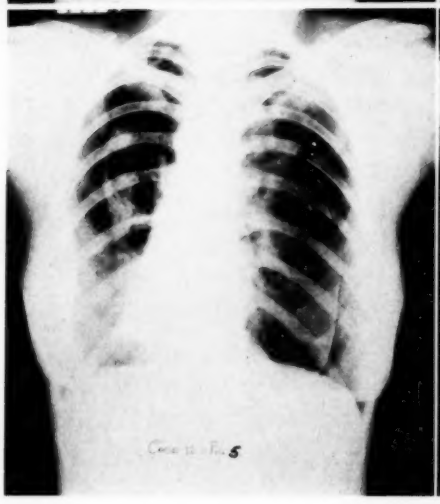

FIG. 5

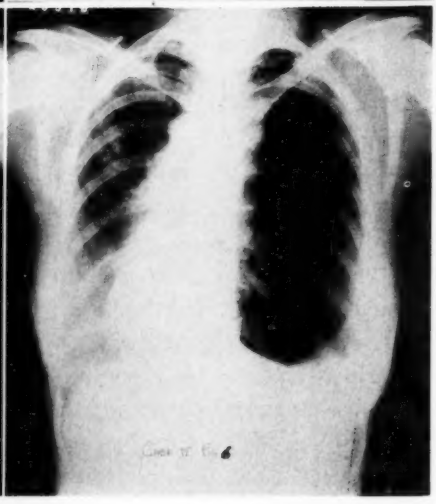

FIG. 6

FIGS. 1–6

reflection of lung is attached. If this is not the case there are times when it is desirable to infiltrate the subpleural tissue with 4 or 5 cc. of novocaine, and to obtain a degree of bulging in this way. The parietal pleura is then carefully incised with the cautery or high frequency current around approximately half the circumference of the adhesion. Then by cold dissection in the subpleural space the adhesion or reflection of lung is gently peeled down until the pleura is visualized on the opposite side. This is then severed. In difficult cases several operations may be required to complete the enucleation. The procedure is tedious and time consuming, but the utilization of this method substantially increases the usefulness of pneumonolysis. An alternate procedure for dealing with adhesions that contain lung tissue and possibly blood channels is that of electrocoagulating the chest wall attachment of the adhesion. Sometimes within a few days the adhesion will elongate sufficiently to make an effectual pneumothorax. Matson claims that this surpasses every other method in dealing with adhesions of this type and with particular reference to the "funnel" and "spool" variety.

METHODS OF SEVERING ADHESIONS

With reference to general technique, the two-puncture method, similar to that used by Jacobaeus in 1913, remains the procedure of choice. The single puncture method, such as used by Singer in 1924 and improved by Davidson in 1929 and Cutler in 1932, is not extensively employed. The Cutler "operating forceps thoracoscope" is designed to permit visualization and severing of adhesions through the one instrument. Adhesions are grasped in forcipated jaws, coagulated and cut by a high frequency current. A McCarthy foroblique telescope is a component part of the instrument, but transilluminating telescopes employing either the foroblique or right angle visual systems are also available for thoracoscopic

FIG. 1. Case 1. Ineffectual pneumothorax of six weeks' duration. Thoracoscopic examination revealed a direct attachment of lung to the parietal pleura. This was enucleated without complication.

FIG. 2. Case 1. Cavity became closed immediately and sputum negative.

FIG. 3. Case 2. Bilateral cavitation

FIG. 4. Case 2. Left pneumothorax of four months' duration. Nine adhesions severed with prompt cavity closure.

FIG. 5. Case 2. Effectual left pneumothorax. Right pneumothorax of three months' duration.

FIG. 6. Case 2. Result after enucleation and division of extensive complex adhesions requiring five operations. Left lung reëxpanded. Cavities closed and sputum negative. Patient very well and able to work.

examination. An accessory instrument without jaws is used for short adhesions and apical bands. The cannula is eight inches long and calibrated 26 Fr.

With the Jacobaeus technique adhesions are burned with the galvanocautery. The thoracoscope is introduced posteriorly or anteriorly as preferred and the galvanocautery at the most suitable site as determined by the position of the adhesions. This is commonly in the anterior axillary line. The cautery tip should have a faint red glow in a darkened room and cauterization must proceed slowly to insure adequate coagulation. The original Jacobaeus thoracoscope has since been improved upon, notably by Unverricht in 1922. Unverricht also developed a flexible cannula through which a curved cautery could be introduced. A variety of cautery shafts and tips have been devised to meet individual requirements. The Coryllos thoracoscopic unit is among the most generally useful for the galvanocautery method. It includes a foroblique telescope, a light carrier, cautery electrodes of two lengths and a cautery handle equipped with a switch. A cautery and light transformer are built into one end of a compact instrument case. The cannulae are metal, nonflexible and about three inches long with a calibre of 19 Fr. The lamp and the telescope move independently of each other. Thus with the light in a fixed position near an adhesion, the telescope may be moved closer for magnification or at a distance for a wide-field view. The lamp is readily kept off the field of vision. For electrosurgical severing of adhesions accessory electrodes are available to pass through the Coryllos cannula. These, like the cautery electrodes, have a straight shaft. Julian Moore's instruments are modelled after those of Jacobaeus, with modifications for the electrosurgical method. Included are a straight and a curved shaft with interchangeable ball, blade and pointed electrodes. The cannulae are of small calibre and flexible. Moore's thoracoscope is of the right angle type with light attached, but gives a wider field of vision than that of Unverricht. Matson's instruments are preferable to all others for the electrosurgical division of adhesions. One electrode is flexible; the distal two inches of the shaft can be flexed to approximately 45° from the long axis by turning a fluted disc on the instrument handle. Long and short extensions may be added if required. A second electrode is jointed. By turning the handle disc the operating tip can be angulated up to 45°. As with Moore's set there are interchangeable ball, blade and pointed electrodes. The cannulae are two and two and one-half inches long, of narrow gauge and made of bakelite.

Matson uses the Bovie electrosurgical unit and the Unverricht or Moore thoracoscope.

Our experience is based on the use of the Coryllos galvanocautery set, Matson's and Moore's instruments with the Bovie electrosurgical unit and the Cutler operating forceps thoracoscope with a vacuum tube type of high frequency machine. Only a few operations were done with the latter, but impressions were unfavorable. The advantage of using one cannula is apparent rather than real. In fact two small cannulae are preferable to one large one. On occasion we have inserted a third cannula and have never noted any ill effect. Contrary to what might be supposed it is no easier to manipulate the single instrument thoracoscope than it is to use the thoracoscope in one hand and the instrument in the other. Due to the fact that these fit snugly into their respective cannulae no great degree of ambidextrousness is required. Any possible advantage of the single puncture method was offset, in our cases, when it was found that repeat operations were more often required due to a more limited operative field. This was particularly true when the cannula was introduced too close to an adhesion to permit its being grasped. In the two-puncture method an interchange of telescope and instruments overcomes this difficulty.

COMPARISON OF ELECTROSURGICAL AND GALVANOCAUTERY METHODS

Wide difference of opinion exists as to the relative merits of galvanocautery and electrosurgery in the severing of adhesions by the two-puncture technique. Jacobaeus and Unverricht have had more experience with pneumonolysis than any others, and although they have used the electrosurgical method they soon reverted to the galvanocautery. Matson is the foremost advocate of the electrosurgical method. Maurier (4) reports the use of high frequency current for coagulation and the galvanocautery for the division of adhesions. The disadvantage of the electrosurgical method is that it is relatively complicated. It is easy to bring the cautery to the proper heat, but it is definitely more difficult to decide upon the proper settings on the electrosurgical unit for coagulation and cutting in the various types of adhesions. The ability to determine the optimum current comes only after considerable experience. Once this has been gained, however, we are in accord with Matson's claims for the superiority of the method. The simpler adhesions can be severed readily and with little danger by either method, but for the more complex type containing reflections of lung tissue the electrosurgical procedure

is undoubtedly preferable. Electrocoagulation is far superior to the coagulation obtained with the cautery, and by its use bleeding in thick vascular adhesions can be prevented. When bleeding does occur it can be controlled more readily. Either superficial or deep coagulation may be obtained depending upon the intensity of the current used. For adhesions that are otherwise inoperable because of lung parenchyma extending to the chest wall, electrocoagulation of the parietal pleural attachment is usually followed by lengthening of the adhesion or in some cases by its separation. The cutting of the adhesions with the high frequency current is precise, and there is no smoke or radiating heat. The instrument shaft does not become hot as is the case with the cautery and accordingly possible injury to the lung through contact with the shaft is avoided. It has been reported (5) that pain is a prominent feature of this method, but this has not been our experience. Pain is experienced in some degree just as it is with the cautery and occasionally, it is true, a patient complains of a "shock" or muscular spasm which may be severe enough to cause him to jerk suddenly on the table. In such a case we prefer—if the adhesion is suitable—to substitute the cautery but otherwise the parietal pleural attachment of the adhesion is anaesthetized by means of a long needle introduced through one of the cannulae. In this way all pain can be overcome. Occasionally we have been unable to complete the division of an adhesion with the high frequency current because of carbonization and consequent defective conduction of the adjacent tissue. This is due to error of judgment rather than deficiency of the method, but in such cases the separation of the adhesion may be completed with the cautery. In our series complications were fewer with the electrosurgical method than with the galvanocautery.

RESULTS OF PNEUMONOLYSIS

One hundred and fifteen patients had 163 operations; 62 patients had one operation, 26 had two operations and the remainder required up to five operations. Twenty-seven patients received bilateral pneumothorax treatment and adhesions were severed on both sides in 5 of these. The galvanocautery was used for 76 operations and the high frequency current for 70. Twenty-four adhesions were enucleated by the cold cautery technique. A total of 356 adhesions were severed in 98 patients, an average of nearly 4 per patient. These were made up of 203 strings and cords, 129 bands and 24 of a complex type such as spool- and cone-shaped adhesions. Ninety-seven patients were classified as far advanced and

18 as moderately advanced. Sputum was positive and one or more cavities were present in 108 patients. Pneumonolysis was done on 3 patients who had an effectual collapse but who were gradually losing their air space because of contraction of adhesions. One patient had a large left-sided pneumothorax but the downward pressure on the diaphragm appeared to be responsible for gastric irritability and a serious loss of weight. Even slight coughing caused vomiting. Division of adhesions with a consequent more selective collapse completely relieved the gastric symptoms.

Altogether 7 patients had negative sputum and cavity closed before operation. An improved and more selective collapse was obtained in each case following division of adhesions. Sputum conversion and cavity closure was effected in 76 patients. No attempt was made to sever adhesions in 17 patients because of their inoperable nature. In the remaining 15 an unsuccessful attempt was made to free adhesions of a complex type. Operative success accordingly approximates 85 per cent if the 17 thoracoscopies are excluded and 72 per cent if they are included. No attempt has been made to give an exhaustive analysis of results. The value of the operation is in its effect on the pneumothorax and end results must be considered under the subject of pneumothorax. It is perhaps admissible to state here that the expectation of a favorable issue to the pneumothorax following pneumonolysis is at least equal to an effectual pneumothorax without pneumonolysis. In this connection the recently published results by Hjaltested and Torning (6) of 191 completed pneumothoraces are of significant interest. The authors state that the results are twice as good in cases free from adhesions, spontaneously or after cauterization. They advocate severing of adhesions in many cases even though sputum is negative and cavity closed.

Following most operations there was commonly a slight rise of temperature and a mild degree of emphysema. Pleural effusion was the most common complication occurring in 10 patients but in each case the fluid resolved following one or more aspirations. Transient serous exudates in the costophrenic sinus are not included. Tuberculous empyema complicated the operation in 4 cases; 2 were successfully treated with oleothorax and 2 underwent thoracoplasty. One patient developed a staphylococcal empyema following operation and died within six months. Death was directly attributable to the pneumonolysis. Five other patients are dead but for reasons not associated with pneumonolysis. Severe bleeding was not encountered. Complications were fewer with

the electrosurgical method, only one case of tuberculous empyema and 3 serous exudates occurring in 70 operations. This contrasts with 7 serous exudates, 3 cases of tuberculous empyema and one staphylococcal empyema in 76 operations with the galvanocautery.

SUMMARY

Indications for closed intrapleural pneumonolysis with a comparison of the Jacobaeus and electrosurgical procedures have been described. The effect of adhesions on 400 pneumothoraces before the availability of pneumonolysis has been briefly analyzed. The results of 163 operations on 115 patients have been discussed.

CONCLUSIONS

1. Adhesions may be severed with relative safety even though the duration of pneumothorax is short.
2. Where adhesions prevent a satisfactory pneumothorax their division brings about an effectual collapse in a high percentage of cases.
3. The scope of pneumonolysis is widened by utilization of the enucleation technique.
4. The electrosurgical method is superior to the galvanocautery for severing adhesions of a complex type.

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PLEURAL SENSITIVITY TO PROCAINE

K. M. SODERSTROM[1]

Disagreeable reactions to pneumothorax refills are a rather common disturbing factor. There are a certain few patients, who, for no other reason than severe refill reactions, are forced to the abandonment of this valuable procedure. These reactions, frequently referred to as "gas reactions," "pneumothorax reactions" or "refill reactions," are probably due to several different causes. Some of these symptom complexes have been termed "pleural shock," which usage is becoming less common, limiting that expression to a rarer and more serious complication. Theories as to the cause and correction of these refill reactions may be applicable in one instance and of no value for the alleviation of the disturbance in a group of other reactors.

Positive pressures, too large refills, prolonged interval between refills, the presence of adhesions and a generally poor technique are the usual causative factors given as explanations of these reactions. In the writer's experience and observations, remedies patterned upon corrections or alterations of these factors have only occasionally shown gratifying results. There are too many similar cases receiving the same amounts of air at refills with the same time interval and same technique who get no reaction, to lend much support to these explanations as the likely cause of all or most refill reactions. The fact that adhesions exist in the majority of pneumothorax cases, as revealed by X-ray and more certainly by the thoracoscope, makes one dubious about blaming the presence of adhesions in an isolated case as the cause of his reactions. Generally, poor technique in any phase of surgery is apt to produce reactions.

It would seem, then, that there is room for new explanations for some of these troublesome reactions. Based upon the theory of sensitivity, or possibly allergy, the writer has the belief that the pleura can develop a sensitivity to procaine and this sensitivity be the true cause of many of our refill reactions. The allergist refers to a tissue of the body in which a hypersensitivity develops as a "shock-organ." This may be the con-

[1] State Department of Health, Seattle, Washington.

junctiva, nasal mucous membrane, bronchial mucous membrane, and probably the most common "shock-organ" of all, the skin. In pneumothorax we have exposed a membrane to elements never so intended by nature. It would seem then, if elsewhere in the body membranes normally exposed to external elements develop a sensitivity to certain usually innocuous agents causing those agents to become irritants, that the pleura likewise could be expected to develop such a reaction. We usually think of the development of hypersensitivity, or the creation of an allergy, as due to a protein or protein fraction. This is true in most hypersensitive and allergic states, but we know that there are certain cases of sensitivity to chemicals, both organic and inorganic in nature. Certain benzene ring compounds have been repeatedly shown to be able to create a specific sensitivity (1). Procaine has a benzene ring in its structural formula. Experience has taught the surgeon that a patient who once reacted well under a given local anaesthesia may at a later date be found to be quite sensitive to that same chemical agent. Dental surgeons particularly have noted this fact. This experience is particularly true in the use of procaine and has been ably described and summarized recently by Gilman (2). In surveying the literature one finds several articles of fairly recent publication on the subject of hypersensitivity to allergens that are nonproteins (1, 3, 4, 5). Waldbott (3) emphatically states that "nonallergens" (substances nonprotein in nature) can create an allergy. Landsteiner and van der Scheer (6) write that antigens may be of simple constitution yet react as of protein complexity. McKay (5) describes pneumothorax reactions as due to novocaine, but in his cases attributes it to a systemic development of sensitivity to the novocaine. One of his pneumothorax cases developed asthmatic symptoms following each refill. In summary he states, "In the light of subsequent events it seems reasonable to assume that the reaction was due to novocaine. The question is also raised as to whether certain unpleasant after-effects complained of by patients generally, who are receiving artificial pneumothorax treatment, may not be due to novocaine or similar products used in conjunction with the treatment rather than to the treatment *per se*."

The writer first thought of the possibility of the pleura developing a sensitivity to procaine in 1936 when troubled with a case that gradually developed severe refill reactions. This case is illustrative of the symptom complex of most of our refill reactions and will serve as a study of the problem.

Case Report

Mr. S., age 30, white, had pneumothorax on the right instituted in Colorado on June 25, 1935 for a unilateral tuberculosis, moderately advanced. The initial collapse was accomplished in the usual way with procaine anaesthesia. The following day his first refill was given and this without use of anaesthesia as were all subsequent refills. This procedure was routine at his institution of first hospitalization. For fourteen months he received weekly refills of moderate amounts without the slightest reaction to any of them. An excellent free space was created with the initial collapse and radiographic and clinical improvement was prompt. After about fourteen months of in-patient and out-patient care in this institution, he changed residence to Seattle where he continued his pneumothorax at Firland Sanatorium. At this institution he was given his subsequent refills with similar technique but with the use of procaine anaesthesia. The refill interval was maintained at weekly dates and with the consistent employment of negative pressures. For a few weeks there was no reaction complained of, though later when reactions developed he recalled that from the first date that procaine was used he had an increased pulse rate and an "uneasiness" about the heart, coming on three to four hours after the refill and lasting a few hours. About eight weeks after commencing the use of the local anaesthesia, however, the refill reactions became insiduously and progressively severe. To the increased pulse and "heart consciousness" were added slight fever, slight general malaise and mild, vague discomfort in the right hemithorax. All of these increased in severity after a few more refills until fever as high as 102°F., pulse of 120, excruciating aching pain in the right hemithorax with general malaise were the usual symptoms of his reactions. These complaints lasted three to four days. Finally, the development of fluid in addition to the other complaints seemed to demand that the procedure be stopped. All of this occurred in spite of repeated alterations of technique. It was at this stage, after analyzing his past happy experience with the present, that the conclusion was made that the anaesthesia might play the causative rôle. He had previously shown during the course of his pneumothorax no intolerance to procaine when subjected to a haemorrhoidectomy under local procaine infiltration. This fact had prevented earlier consideration of this possibility. However, this fact notwithstanding, after all symptoms had subsided a few cubic centimetres of 1 per cent procaine solution were injected subcutaneously. No reaction whatsoever followed. The next day 1 cc. of 1 per cent procaine was instilled with a long slender needle directly into the pleural space allowing none to get into the tissues and no air to enter the pneumothorax space. A reaction so severe as to be alarming developed in about four hours, reaching its maximum in twenty-four hours. At this time

any motion causing movement of the chest was attended with excruciating pain in the right hemithorax, breathing was painful, the temperature rose to 103°F. and joint and muscle pains were complained of. Five days later, with the patient not completely recovered, a refill was given with a 20 gauge dry needle and no anaesthesia. No reaction developed and, as a matter of fact, the patient stated an hour later that he felt much better than just before the refill. To-day, two and one-half years later, this patient is still taking pneumothorax and leading a normal active life. Because of his desire to work full hours at tiresome work, pneumothorax has been maintained, although there is apparent healing of the lesion. The pleural fluid promptly resorbed after ceasing the use of procaine and at no time during the ensuing interval has a refill caused any discomfort, nor has fluid developed.

This case has been described in some detail as it is quite typical of the reactions encountered in other patients in the last two and one-half years since then, although the symptoms were more severe and frequent here than in the majority of cases.

At first the procaine-sensitive cases were identified by instilling procaine into the pleural space, but in two of these the reaction was so severe that this test was abandoned in favor of merely discontinuing the use of the anaesthesia. If this change of technique relieved the reactions, it was satisfactory evidence that procaine should be avoided. One case developed fluid to the level of the fourth rib forty-eight hours after such a test dose. Eight weeks later this fluid had resorbed. To date there have been 11 patients relieved of refill reactions at Firland Sanatorium by completely eliminating procaine from the pleural space at the time of refills.

Because it has been found in these particular cases that there are no reactions to the procaine except pleural, it has been possible to use a fine, short needle to anaesthetize the skin and subcutaneous tissues and then with a minimum of discomfort insert a large, dry needle for the refill. This procedure, of course, is not used in a case of systemic hypersensitivity to procaine. A sharp 20 gauge needle can be used with no skin anaesthesia and with only slight pain, if one is satisfied that there is a large enough pleural space to safely permit rather rapid insertion. The accident of getting procaine into the pleural space in the first place was in an attempt to give a painless procedure to the patient. The solution was pushed, with moderate force, in advance of the needle. According to the writer's observations, this technique is most commonly used elsewhere. Any technique that prevents the spilling of procaine

into the pleural space should relieve a patient with this particular sensitivity.

Through personal communications between Dr. F. S. Miller, Medical Director of Edgecliff Sanatorium, Spokane, Washington, and the writer, Doctor Miller reports 4 cases as being relieved of their previous refill reactions by discontinuing procaine anaesthesia. This is convincing proof that the reactions encountered at Firland are not the result of a technique peculiar to this institution.

No attempt has been made in this study to compare the different types of local anaesthesia as it seemed nothing was to be gained. Simply keeping the procaine, even a drop, from the pleural space was all that was needed to rectify the trouble.

SUMMARY AND CONCLUSIONS

That it is possible for the pleura of an individual taking pneumothorax collapse therapy to develop a hypersensitivity to procaine local anaesthesia has been demonstrated by 11 cases observed in the past two and one-half years at Firland Sanatorium.

This demonstration of sensitivity is another that indicts procaine, and probably all local anaesthesias, for being a causative agent or allergen in the development of a specific hypersensitivity in a certain few patients.

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STATISTICAL DATA

Edited by JESSAMINE S. WHITNEY

TUBERCULOSIS DEATH RATE STILL DECLINING

"Tuberculosis is another disease which caused fewer deaths last year than ever before; but in 1939, to date, there has been the still further drop of 4.3 per cent. It is thus already a practical certainty that 1939 will be one more year added to the long sequence during which the mortality from tuberculosis has been continuously decreasing."[1]

CASE-FINDING IN DETROIT

The June issue of the American Journal of Public Health carried a featured article entitled *Results Obtained in an Extensive Tuberculosis Case Finding Program in a Large City* by Bruce H. Douglas, M.D. and Gaius E. Harmon, M.D., which was a paper read before the Epidemiology Section of the American Public Health Association at its 1938 meeting.

In it the authors, both of whom are on the staff of the Detroit Department of Health, summed up to date the findings of the extensive case-finding program under way in that city.

During the first eighteen-month period, 114,831 tuberculin tests were reported, and of these 31,803, or 27.8 per cent, were positive. The results of 27,084 X-ray examinations were reported. Six hundred thirty-three (633) verified cases of tuberculosis were found, or about 2 per cent of the persons having positive tuberculin tests. This 2 per cent included only cases of tuberculosis of such a degree of activity as to call for treatment.

Classified as to whether or not they were contacts or suspects, the figures were as follows:

*Class**	*Per cent positive of total examined*
Contact	40.9
Suspect	32.5
Unclassified	26.5
Total	29.2

* Figures here cover only a fourteen and one-half month period.

[1] Statistical Bulletin, Metropolitan Life Insurance Company, July, 1939.

The distribution by age* showed that the percentage of positive reactors increased with age.

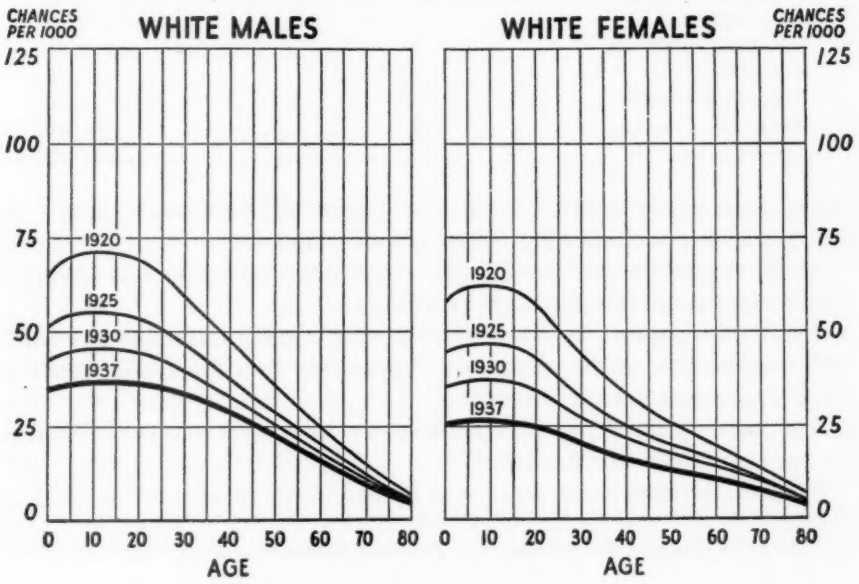
Age	*Total tested*	*Per cent positive*
0–9	20,585	5.9
10–19	22,441	18.9
20–29	21,304	38.0
30 and over	34,862	44.3
Age not stated	222	30.2
Total	99,414	29.2

* Based on a fourteen and one-half month period.

Of the 545 cases of adult type of active tuberculosis discovered, the percentage of minimal cases declined with increasing age.

Age	*Adult type cases, per cent minimal*
0–9	80.0
10–19	37.2
20–29	31.7
30 and over	25.0
Age not stated	100.0
Total	29.9

CHANCES OF EVENTUALLY DYING FROM TUBERCULOSIS



THE CHANCES OF DYING FROM TUBERCULOSIS

We are indebted to the Metropolitan Life Insurance Company[2] for a valuable analysis of the improvement in the tuberculosis mortality figures in recent years. The measure used is the chance of dying from tuberculosis. According to their data, based on United States Census Bureau figures, "the average white person at ages up to 25 has about one chance in 30 of eventually dying from tuberculosis. Barely 20 years ago the chances were twice as great."

The results are summed up in the graph shown on bottom of page 739.

White persons	*Chances of dying from tuberculosis for new-born infants*	
	1937	1920
Males	35 in 1,000	65 in 1,000
Females	25 in 1,000	58 in 1,000

THE GALLUP POLL

A nation-wide survey by Dr. George Gallup, Director, American Institute of Public Opinion, has recently been completed to determine how much the public knows about the cause and cure of tuberculosis.

The first question was "What do you think is the cause of tuberculosis?" The answers:

Germ	18%
Run-down condition	17%
Malnutrition	13%
Poor living conditions	12%
Bad heredity	11%
Exposure to weather	11%
Bad food	8%
Colds	6%

Other causes named included weak lungs, impure air, too much drinking, wet feet, cattle, too much smoking, worry, lack of vitamins.

The next question was "Do you think tuberculosis is contagious (catching)?" Twenty-four per cent replied in the negative.

The third question was "Do you think tuberculosis is inherited at birth?" Fifty-two per cent of the voters in the survey say they think it is inherited, while 48 per cent think it is not.

The fourth question was "Do you think tuberculosis is curable?" Eighty-six per cent answered affirmatively.

The final question in the survey was "What do you think is the best way to

[2] Statistical Bulletin, Metropolitan Life Insurance Company, August, 1939.

cure tuberculosis?" Some voters mentioned more than one method of treatment, and the aggregate vote for each of the leading cures mentioned is:

Rest	43%
Proper diet	36%
Fresh air	26%
Climate	25%
Sanatorium treatment	13%

Other cures suggested by small groups of voters included sleeping outdoors, collapsing the lungs, high frequency current, drinking plenty of milk, and "going to the woods."

TUBERCULOSIS DEATHS IN INSTITUTIONS

In the October issue we referred briefly to a report[3] of the United States Bureau of the Census entitled *Deaths in Hospitals and Institutions* and quoted certain figures on tuberculosis from that report. A further analysis of this unique report reveals other interesting data concerning mortality from tuberculosis which heretofore have not been available.

A classification of tuberculosis deaths in "hospitals and institutions," according to large geographical groups, gives the following results:

Geographical areas	*Percentage of total tuberculosis deaths occurring in institutions*
Far west	68
Northeast	64
Middle states	57
Northwest	49
United States	48
Southwest	28
Southeast	22

To a certain extent these percentages reflect the provision of tuberculosis beds in the various areas, although "hospitals and institutions" include general and special hospitals of other sorts and mental, penal and other resident institutions.

A differentiation by sex shows that 53 per cent of male deaths and 39 per cent of female deaths (respiratory tuberculosis only) occurred in institutions.

Further analysis by color is limited to 15 states and the District of Columbia, where the Negro population is relatively large. Thirty-four per cent of all deaths (respiratory tuberculosis only) among whites and 28 per cent among other races were in institutions.

[3] Deaths in Hospitals and Institutions, Vital Statistics—Special Reports, Department of Commerce, June 14, 1939.

Classified by type of control of institutions, the figures are as follows:

Institution (type of control)	*Per cent of tuberculosis (respiratory) deaths in institutions*
Total	100.0
Federal	3.9
State, city, county	32.2
Nonprofit	8.1
Proprietary	1.5
Other	1.4
No institution	52.9

THE AMERICAN TRUDEAU SOCIETY

SCOPE AND OBJECTIVES

The American Trudeau Society came into being June 26, 1939 when the American Sanatorium Association met in Boston and by formal action adopted a new Constitution including this change in name. The reorganization preserves the original objectives and spirit of the American Sanatorium Association which was organized in 1905. The scope, however, is enlarged, and the Constitution provides not only for membership drawn, as originally, from physicians engaged in sanatorium work, but also for the inclusion of private practitioners and others who are interested in tuberculosis, diseases of the chest and related conditions. This change was prompted by the widening interest among physicians in this branch of medicine and the growing practice of treating such diseases not only in sanatoria but also in general hospitals, clinics and the home. Since one of the major purposes of the Society is to provide for an interchange of knowledge between physicians and to promote medical education in this branch, the reorganization provides the means by which this purpose can be pursued more adequately.

The Constitution includes various changes defining the objectives of the Society, the internal organization and the types of membership. Printed copies have been distributed to members and are available to others who may be interested.

The long-standing policy of close coöperation with the National Tuberculosis Association is reaffirmed by the Constitution and is to be effected in several specific ways. The members of the Society will act on occasion to advise the National Association concerning its medical policies and activities, and joint committees will be set up when indicated to serve in this capacity. The American Trudeau Society will have responsibility for planning and conducting the medical programs at the Annual Meeting which will be held jointly as heretofore with the National Association. This eliminates the former plan of holding separate meetings and should make for improvement in the medical section. Likewise, the address of the American Trudeau Society is 50 West 50 Street, New York City, which is also the headquarters of the National.

OFFICERS

The Constitution provides for officers, a Council, an Executive Committee and various other committees. Elections conducted at the Boston Meeting

and appointments made by the Council resulted in the designation of the following incumbents for the current year.

Dr. J. Burns Amberson, Jr., N. Y., President
Dr. L. J. Moorman, Okla., President-Elect
Dr. John B. Barnwell, Mich., Vice-President
Dr. Benjamin L. Brock, Ky., Secretary-Treasurer

Council

(in addition to the four officers)

Dr. G. C. Bellinger, Ore.
Dr. Robinson Bosworth, Ill.
Dr. Ezra Bridge, N. Y.
Dr. Chesley Bush, Calif.
Dr. H. J. Corper, Colo.
Dr. Victor F. Cullen, Md.
Dr. Bruce H. Douglas, Mich.
Dr. E. W. Hayes, Calif.
Dr. Arthur T. Laird, Minn.
Dr. D. O. N. Lindberg, Ill.
Dr. Paul P. McCain, N. C.
Dr. Edward J. Murray, Ky.
Dr. Edward N. Packard, N. Y.
Dr. Leroy S. Peters, N. M.
Dr. Henry C. Sweany, Ill.

Executive Committee

Dr. J. Burns Amberson, Jr., N. Y.
Dr. John B. Barnwell, Mich.
Dr. Ezra Bridge, N. Y.
Dr. Benjamin L. Brock, Ky.
Dr. Bruce H. Douglas, Mich.
Dr. L. J. Moorman, Okla.

Medical Program Committee

Dr. John Alexander, Chairman
Dr. Arthur Vorwald
Dr. George G. Ornstein
Dr. Emil Bogen
Dr. Paul P. McCain
Dr. H. Frank Carman

Membership Committee

Dr. Harold Trimble, Chairman
Dr. Henry C. Sweany
Dr. Hugh B. Campbell

Nominations Committee

Dr. S. A. Slater, Chairman
Dr. Everett Morris
Dr. W. Atmar Smith

X-ray Apparatus and Technique Committee

Dr. F. M. McPhedran, Chairman
Dr. C. B. Gibson
Dr. W. L. Rathbun
Dr. J. L. Wilson
Dr. Ezra Bridge
Dr. D. O. N. Lindberg
Homer L. Sampson, Sc.D.
Dr. Henry D. Chadwick
Dr. G. S. Pesquera
Dr. J. C. Walsh

Standard Laboratory Procedures Committee

Dr. Henry C. Sweany, Chairman
Dr. Max Pinner
Dr. H. S. Willis
Dr. Emil Bogen

MEMBERSHIP

The Constitution provides for two classes of members. Junior memberships are designed for graduates in medicine who have recently entered the field of clinical tuberculosis. They may continue for five years from the date of the member's graduation in medicine. The dues are $5.00 per year which includes membership also in the National Tuberculosis Association. Junior members may subscribe to the American Review of Tuberculosis at the reduced rate of $7.00 per year. Active members include all those not in the junior class, and the dues are $12.00 a year which includes membership also in the National Tuberculosis Association and a year's subscription to the American Review of Tuberculosis. The American Review of Tuberculosis is designated as the official journal of the Society. The Membership Committee is now active in arranging for members of the previous American Sanatorium Association to continue in the American Trudeau Society so that the transition should be fully accomplished on or about the first of the coming year. The Membership Committee is also ready to receive applications from others who wish to join the Society. Information and application forms may be obtained by applying at the address given above.

The Executive Committee of the Society plans to meet during the winter to take up matters which need attention.

ANNUAL MEETING 1940

The next meeting of the American Trudeau Society in conjunction with the National Tuberculosis Association will be held in Cleveland, Ohio, June 3 to 6, 1940. The American Association for Thoracic Surgery will also meet in Cleveland June 6, 7 and 8 and a joint meeting of the societies is being arranged to occupy all of Thursday June 6. It will be noted that the meeting of the American Medical Association in New York City will start the following Monday, June 10.

The Program Committee of the American Trudeau Society met under the chairmanship of Dr. John Alexander with the Program Committee of the National Tuberculosis Association under the chairmanship of Dr. Henry D. Chadwick in Cleveland, September 17, and preliminary plans were drafted for the coming meeting. In addition to the joint meeting with the American Association for Thoracic Surgery, other special features planned include a joint session with the administrative section of the National Tuberculosis Association, Wednesday, June 5, and clinics to be conducted in the Cleveland hospitals by local physicians on Tuesday and Wednesday afternoons, June 4

and 5. The X-ray Conference will be modified somewhat from the plan followed at previous meetings but will be held as usual on Wednesday evening. This will be a diagnostic and therapeutic clinical conference, emphasizing the use of the X-ray. At the close of one of the afternoon meetings a forum will be conducted at which questions previously submitted by members will be brought up in informal discussion, an innovation which should prove highly interesting. On one of the evenings of the meeting it is planned to present a clinic for Cleveland practitioners in coöperation with one of the local medical societies. The formal session of the Society will provide for fewer papers (about four at each session) but longer discussions in which members will be encouraged to participate.

The program is now being organized and any member who wishes to submit a title should write immediately to Dr. John Alexander. Dr. Alexander's address until December 31, 1939 will be University Hospital, Ann Arbor, Michigan; after January 1, Estancia del Sol, P.O. Box 2029, Tucson, Arizona. The closing date for applications for places on the program is February 1, 1940.

Information concerning the activities of the Society, a circular descriptive of its work, and copies of the Constitution may be obtained by addressing the American Trudeau Society, 50 West 50 Street, New York City.

NOTE

BIOLOGICAL ABSTRACTS

The Editor of *Biological Abstracts* announces a new section, *Bioclimatology —Biometeorology*, which will in the future form a part of a section of *Ecology* in *Biological Abstracts* and which will be under the editorship of Mr. Robert G. Stone of the Blue Hill Observatory, Harvard University.

It seems hardly necessary to point out to the readers of the REVIEW that the reawakened interest in the biological influences of climatic and meteorological factors is reflected in many scientific studies directly concerned with tuberculosis and respiratory diseases. We wish, therefore, to draw the attention of our readers to this new abstract section which will undoubtedly contain references to our special field of interest, frequently collected from publications not usually read by physicians.

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